

AMERICAN HEART JOURNAL

For the Study of the
CIRCULATION



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PUBLISHED MONTHLY

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VOLUME 24

JULY—DECEMBER, 1942

ST. LOUIS

THE C. V. MOSBY COMPANY

1942

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Printed in the
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*Press of
The C. V. Mosby Company
St. Louis*

American Heart Journal

VOL. 24

JULY, 1942

No. 1

Original Communications

AGE AND AURICULAR FIBRILLATION AS INDEPENDENT FACTORS IN AURICULAR MURAL THROMBUS FORMATION

WILLIAM E. HAY, M.D., AND SAMUEL A. LEVINE, M.D.
BOSTON, MASS.

AURICULAR mural thrombi have been found in most forms of heart disease, and are known to be particularly common in rheumatic heart disease. That their presence or absence has a marked bearing on the span of life cannot be denied. Weiss and Davis¹ have shown that rheumatic heart disease, more than any other form, is responsible for embolic manifestations. In this kind of heart disease there are several possible factors that play a part in their formation, i.e., the duration of the rheumatic heart disease, the presence of congestive failure and its duration, the presence of mitral stenosis, auricular fibrillation, persistent rheumatic inflammatory activity within the heart, and age.

Levine and Harvey,² in a study of uninfected mural thrombi, selected a group of thirty-one cases in which there was definite evidence of auricular fibrillation, with the idea of showing the effect of auricular fibrillation on the site of thrombus formation. Ninety per cent of those patients had auricular mural thrombi. In comparing them with eighty patients who had regular rhythm and mural thrombi, they found that only 54 per cent of the latter had thrombi in the auricles. Weiss and Davis,¹ in a study of 164 cases of rheumatic heart disease, selected 131 cases in which the rhythm had been accurately ascertained. There were ~~seventy-four~~ patients, or 57 per cent, who had persistent auricular fibrillation, paroxysmal fibrillation, or flutter. They found that 88 per cent of those with extensive auricular thrombi had auricular fibrillation. Graef, et al.,³ in reviewing 178 cases of rheumatic heart disease, found twenty-four, or 13 per cent, in which there were auricular thrombi. They concluded that certain conditions favored the development of auricular thrombi in rheumatic heart disease, among which were severe

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston.
Received for publication Jan. 29, 1942.

mitral stenosis, congestive heart failure, auricular fibrillation, and continued local inflammation. Likewise Garvin,⁴ in a study of 116 cases of rheumatic heart disease, found that mural thrombi were more common among the patients with auricular fibrillation (43.3 per cent) than among those with regular rhythm (18 per cent). He also has shown that in rheumatic heart disease mural thrombi are more common in the older patients.

All of the above investigators were of the opinion that auricular fibrillation plays a part in the formation of auricular mural thrombi. Inasmuch as it will be shown below that patients with rheumatic heart disease with fibrillation are distinctly older than those with regular rhythm, it is clear that all of the above studies need to be reconsidered with due control of the age factor. The important question is whether patients of the same age, with similar valve lesions, will have a different incidence of mural thrombi, depending on whether auricular fibrillation is present or not. As far as is known, this type of analysis has not previously been made. Is there an age factor at all, and, if there is, is it large or small?

TABLE I

	NO. OF CASES	NO. REGULAR RHYTHM	<i>at death</i> AV. AGE REGULAR	THROMBI WITH REGULAR RHYTHM	NO. OF CASES OF AURICU- LAR FIBRILLA- TION	AV. AGE AURICU- LAR FIBRILLA- TION	THROMBI WITH AURICU- LAR FIBRILLA- TION
Under 40 years	75	45	25.9	4 (8.8%)	30	26.7	10 (33.3%)
Over 40 years	111	35	55.3	7 (20.0%)	76	53.2	42 (55.2%)
Total	186	80 <i>42.9%</i>	38.7	11 (13.8%)	106 <i>57.1%</i>	45.7	52 (49.0%)

A study was therefore conducted of the post-mortem records of the Peter Bent Brigham Hospital in all cases of mitral stenosis, with or without other valvular disease (cases of bacterial endocarditis were excluded). The data for the following analysis are summarized in Table I. There were 186 cases, in 106 of which, or 57.1 per cent, auricular fibrillation was present. Regular rhythm was present in eighty, or 42.9 per cent. The average age at death of the patients with regular rhythm was 38.7 years, whereas, in the group with auricular fibrillation, the average age at death was 45.7 years. In the group with regular rhythm there were eighty patients, and eleven, or 13.8 per cent, had mural thrombi. In the group with auricular fibrillation there were 106 cases, in fifty-two, or 49 per cent, of which, mural thrombi were present. The above analysis confirms what other authors have shown, i.e., that mural thrombi are much more common in fibrillators than in patients with regular rhythm. But it also shows that the former are, on the average, seven years older than the latter, and therefore had a longer time for the development of mural thrombosis.

In order to ascertain the part that age played in the formation of mural thrombi, it was necessary to divide the patients into two groups, namely, those 40 years of age and over, and those under 40 years of age. In the group 40 years of age or over, the average age at death in the cases of regular rhythm was 55.3 years. In those of auricular fibrillation the average age at death was 53.2 years. These two groups are now comparable as far as age is concerned, and differ only in cardiac rhythm. There were thirty-five patients with regular rhythm who were 40 or more years of age, and seven, or 20 per cent, had mural thrombi. In the similar group with auricular fibrillation there were seventy-six cases, in forty-two, or 55.2 per cent, of which, mural thrombi were present. From this analysis it follows that auricular fibrillation was conducive to the development of auricular mural thrombi entirely independent of the age factor.

In the group under 40 years of age it was found that the average age at death of those with regular rhythm was 25.9 years, and in those with auricular fibrillation it was 26.7 years. In the group with regular rhythm there were forty-five cases, in four (8.8 per cent) of which mural thrombi were present. In the group with auricular fibrillation there were thirty cases, in ten, or 33.3 per cent, of which, mural thrombi were found. Here again it is clear that mural thrombi were four times as frequent in the fibrillators as in those with regular rhythm, although the ages were the same.

The role that age plays as a factor independent of the presence or absence of auricular fibrillation is well indicated by comparing the occurrence of thrombi in the older and younger groups. Amongst those over 40 years of age the incidence of mural thrombi in the fibrillators was 55.2 per cent, and, in those with regular rhythm, it was 20 per cent, whereas in the two corresponding groups of patients under 40 years of age the incidence was 33.3 per cent and 8.8 per cent, respectively. It follows that younger patients, whether the cardiac rhythm is regular or irregular, are less prone to mural thrombosis.

CONCLUSIONS

An analysis was made of 186 cases of mitral stenosis in order to ascertain the respective roles that age and auricular fibrillation play in the production of auricular mural thrombosis. It was found that both the advancing age of the patient and the presence of auricular fibrillation independently increase the incidence of auricular mural thrombosis in cases of mitral stenosis.

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FACTORS INFLUENCING IMMEDIATE MORTALITY AFTER ACUTE CORONARY OCCLUSION

ROBERT M. WOODS, M.D., AND ARLIE R. BARNES, M.D.
ROCHESTER, MINN.

THE problem of prognosis after acute coronary occlusion was given its now accepted and universally recognized significance by Herrick,¹ in 1912, when he showed that acute coronary obstruction is not necessarily immediately fatal. Herrick predicted at that time that patients who had mild forms of the disease and patients who had gained complete functional recovery probably would be encountered. The advance of knowledge of the principles and the practical application of electrocardiography since that time have greatly facilitated the diagnosis of acute coronary occlusion, as well as the cardiac irregularities which may arise subsequent to acute coronary occlusion.

Various authors have written concerning the factors which may influence the prognosis after acute coronary occlusion. Wiggers² was of the opinion that the two most important are the onset of ventricular fibrillation and the onset of failure of the left side of the heart. Blumer³ observed that embolism originating in mural thrombi occurred among 14 per cent of the patients who had myocardial infarcts. Willius⁴ showed that the previous occurrence of coronary occlusion makes the prognosis more grave than it would be if the condition were initial. Brill⁵ believed that an atypical electrocardiogram is an unfavorable prognostic sign. Strong⁶ stated that low blood pressure and particularly low pulse pressure make the prognosis ominous.

NATURE OF PRESENT STUDY

Purpose.—It is the purpose of this paper to evaluate the factors which are present in, or arise subsequent to, acute coronary occlusion, and lead to death either during the acute attack itself or during the first six weeks after the occurrence of the occlusion.

Material.—One hundred twenty-eight unselected patients with acute coronary occlusion who were under our observation were chosen for this study. There are included in this study persons who died very suddenly, either while they were engaged in normal activity or while they were convalescing from some surgical procedure. In such cases a positive diagnosis of acute coronary occlusion was made on the evidence

Abridgement of thesis submitted by Dr. Woods to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

From the Mayo Clinic, Rochester.

Received for publication Oct. 23, 1941.

found at necropsy. Of these 128 patients, sixty-eight survived the acute attack and were still living at the time of this report. The remaining sixty patients died within six weeks after the onset of the acute attack. In the entire series there were 108 males and twenty females, a ratio of 5.4 to 1.

GENERAL CONSIDERATIONS

Incidence of Immediate Mortality.—The incidence of immediate mortality in the respective age groups is shown in Fig. 1 and Table I. The average age for all the patients in the entire series was 55 years; the average age of the patients who lived was 51.3 years, as compared with an average age of 59.2 years for those who died within the immediate period.

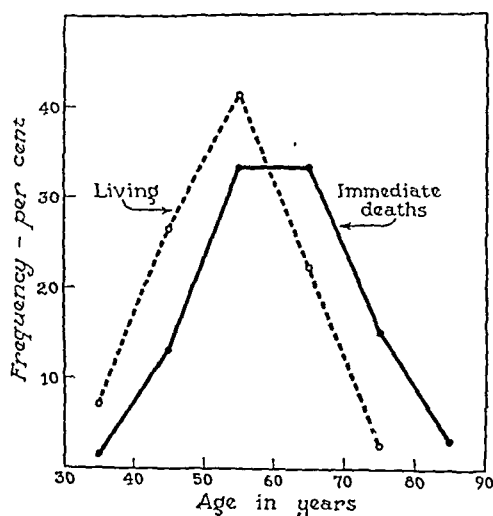


Fig. 1.—The distribution according to age in each series of cases of acute coronary occlusion. The group of living patients includes sixty-eight patients, and the group of immediate deaths includes sixty patients.

TABLE I
INCIDENCE OF IMMEDIATE MORTALITY IN RESPECTIVE AGE GROUPS

AGE (YEARS)	CASES	IMMEDIATE DEATHS	
		NO.	%
Less than 50	32	9	28.1
50 to 59	48	20	41.7
60 to 69	35	20	57.1
70 and more	13	11	84.6
Total	128	60	46.9

TABLE II
INCIDENCE OF IMMEDIATE MORTALITY ACCORDING TO SEX IN TWO MAIN AGE GROUPS

AGE (YEARS)	MEN			WOMEN		
	CASES	IMMEDIATE DEATHS		CASES	IMMEDIATE DEATHS	
		NO.	%		NO.	%
Less than 60	73	25	34.2	7	4	57.1
60 and more	35	20	57.1	13	11	84.6
Total	108	45	41.7	20	15	75

In Table II is shown the incidence of immediate mortality, computed according to sex in the two main groups: patients who were 60 years old or less, and those 61 years old or more.

Relationship of Previous Attacks of Coronary Occlusion.—Fig. 2 shows the relationship of previous coronary artery disease to the outcome in both series of cases.

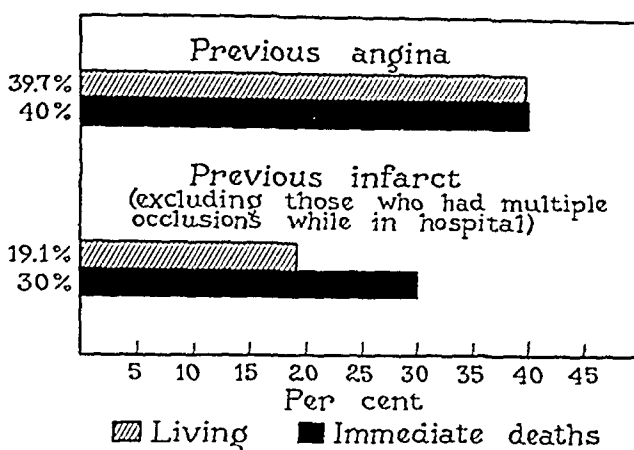


Fig. 2.—Incidence of previous disease of the coronary artery in both series of patients with acute coronary occlusion; that is, those who survived the immediate period after the acute attack, and those who died.

The Effects of Infarction.—In Table III the incidence of the position of the infarct in the respective groups is shown. The position of the infarct was ascertained by examination of the hearts at necropsy, or, in the case of those who survived, was inferred from the electrocardiographic changes when they were sufficiently characteristic to permit localization.

TABLE III

INCIDENCE OF POSITION OF INFARCT (AS LOCALIZED BY THE ELECTROCARDIOGRAM AND SEEN AT NECROPSY)

POSITION OF INFARCT	LIVING AND DEAD		LIVING		IMMEDIATE DEATHS	
	NO.	%	NO.	%	NO.	%
Anterior	62	48.4	36	52.9	26	43.3
Posterior	52	40.6	30	44.1	22	36.7
Unlocalized	11	8.5	2	3	9	15
Multiple	3	2.5			3	5
Total	128	100	68	100	60	100

In an effort to ascertain the influence which the position of the infarct had on the outcome, the patients were grouped as shown in Fig. 3. Of the sixty-two patients with anterior apical infarction, 42 per cent died within the immediate period and the remaining 58 per cent survived the acute coronary occlusion. Of the fifty-two patients with posterior basal infarction, 42 per cent died within the immediate period and the remaining 58 per cent survived the acute coronary occlusion. Of the eleven patients who had an infarct which could not be localized by electrocardio-

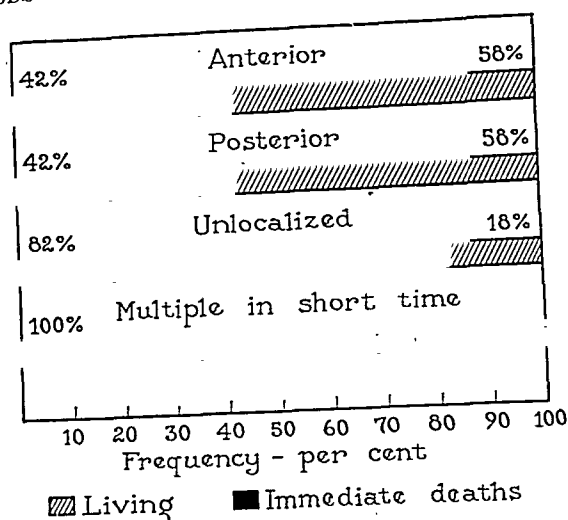


Fig. 3.—The relationship of the position of the infarct to the ultimate outcome. There were sixty-two anterior infarcts, fifty-two posterior infarcts, and eleven unlocalized infarcts. Moreover, three other patients had multiple infarcts within a short period.

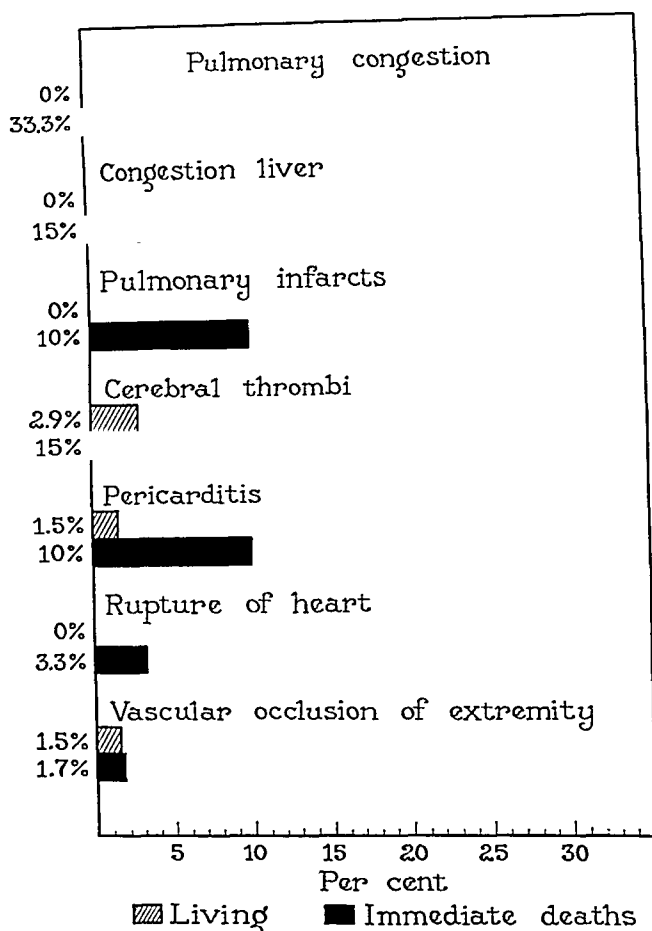


Fig. 4.—Relative incidence of the important complications among both groups of patients; that is, those who survived the immediate period of the acute attack of coronary occlusion, and those who died. These complications all occurred within the first six weeks (immediate period) after onset of the acute attack of coronary occlusion.

graphic evidence, 82 per cent died within the immediate period and the remaining 18 per cent survived. Three of the 128 patients had multiple occlusions while they were under observation in the hospital, and all three died within the immediate period.

Complications After Coronary Occlusion.—Complications which arise secondary to acute coronary occlusion influence to a great extent the immediate prognosis. Fig. 4 shows the relative frequency of the important complications in each series of cases.

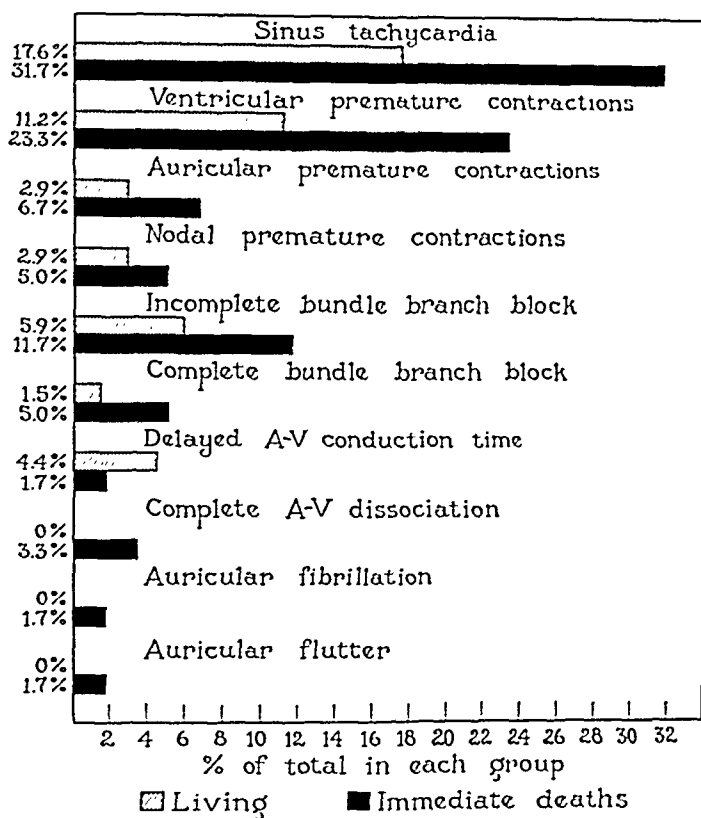


Fig. 5.—Incidence of various cardiac irregularities, as demonstrated in the electrocardiograms of patients in both groups in this series of cases of acute coronary occlusion. None of these cardiac irregularities was known to have been present in any case prior to the acute attack of coronary occlusion.

Cardiac Irregularities.—Whenever possible, electrocardiographic tracings were made at intervals, in an effort to observe changes which would have diagnostic significance and also to help demonstrate any cardiac irregularities which might have developed subsequent to the coronary occlusion and acute myocardial infarction. Fig. 5 shows graphically the incidence of the various cardiac irregularities in each group of this series of patients. The significance of the sinus tachycardia which occurred in nineteen of the patients who died in the immediate period is emphasized by the fact that, ultimately, nine of these nineteen patients developed myocardial decompensation from which they never recovered; in eight of the remaining ten patients, progressively serious cardiac

irregularity developed, and it was assumed that the terminal condition was ventricular fibrillation; the remaining two patients died of pulmonary embolism.

TABLE IV
RELATIONSHIP OF VENTRICULAR EXTRASYSTOLES TO IMMEDIATE DEATHS

FREQUENCY OF EXTRASYSTOLES	NO. OF CASES	LIVING %	DEAD %
Occasional (1 in 21 cardiac beats)	3	100	0
Moderately frequent (1 in 11 to 1 in 20 cardiac beats)	3	100	0
Very frequent (1 in 2 to 1 in 10 cardiac beats)	17	17.6	82.4

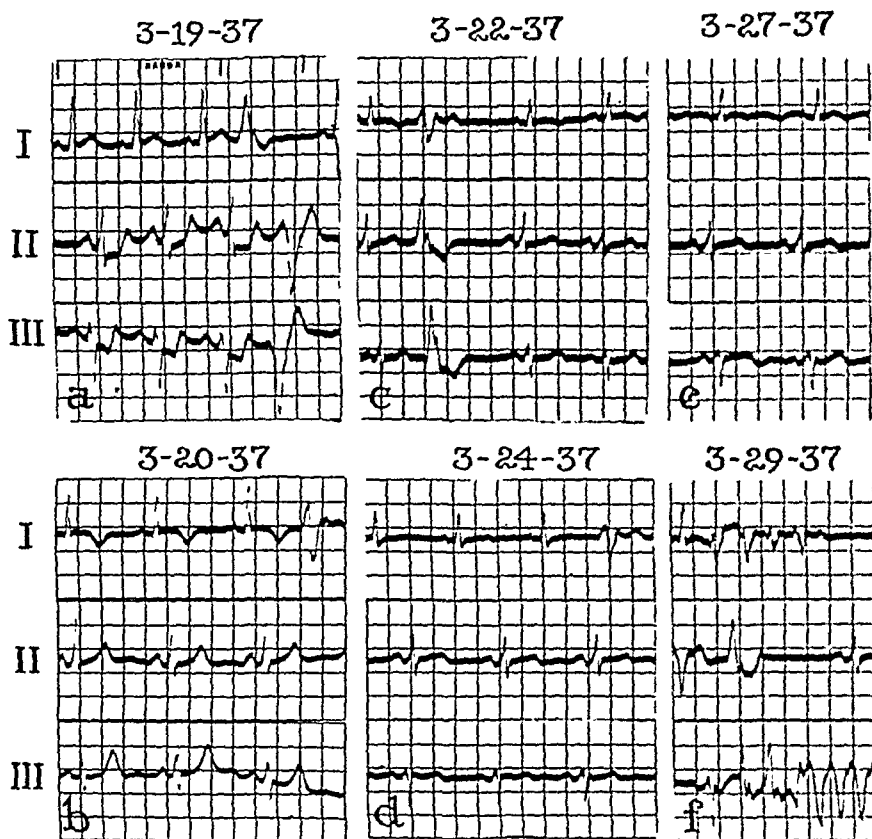


Fig. 6.—a, Electrocardiogram made several days after the patient had had an acute attack of coronary occlusion; there was one ventricular extrasystole in every four beats on March 19, 1937; b, on March 20, 1937, there was only one ventricular extrasystole in the entire record; c, on March 22, 1937, the ventricular extrasystoles became more frequent (once in every five beats); d, on March 24, 1937, the ventricular extrasystoles became still more frequent (once in every four beats); e, on March 27, 1937, none of the ventricular extrasystoles seen in the previous tracings were visible; f, on March 29, 1937, there were frequent series of varying lengths of consecutive ventricular extrasystoles. This patient died March 30, 1937.

Judging from the work of Fishberg,⁷ Fromet,⁸ Mahaim,⁹ Lisa,¹⁰ and many other observers, we may assume that the occurrence of ventricular extrasystoles after acute coronary occlusion is an ominous sign. Ventricular extrasystoles were demonstrated electrocardiographically in 11.2

per cent of the patients who lived, and in 23.3 per cent of the patients who died within the immediate period. In an effort to ascertain further the significance of these ventricular extrasystoles, their relative frequency was studied. Table IV gives the results. Ventricular premature contractions were considered to be "occasional" if they occurred only once in every twenty-one beats, or more. Ventricular premature contractions of occasional frequency developed in three patients, and all survived. Ventricular premature contractions were considered to be of "moderate" frequency if they occurred between once in every twenty beats and once in every eleven beats. Ventricular premature contractions of moderate frequency developed in three patients, and none of them died. Ventricular premature contractions were considered to be "very frequent" if they occurred between once in every ten beats and once in every two beats. Ventricular premature contractions which were considered to be very frequent developed among seventeen patients. Fourteen of these patients (82.4 per cent) died and three (17.6 per cent) survived.

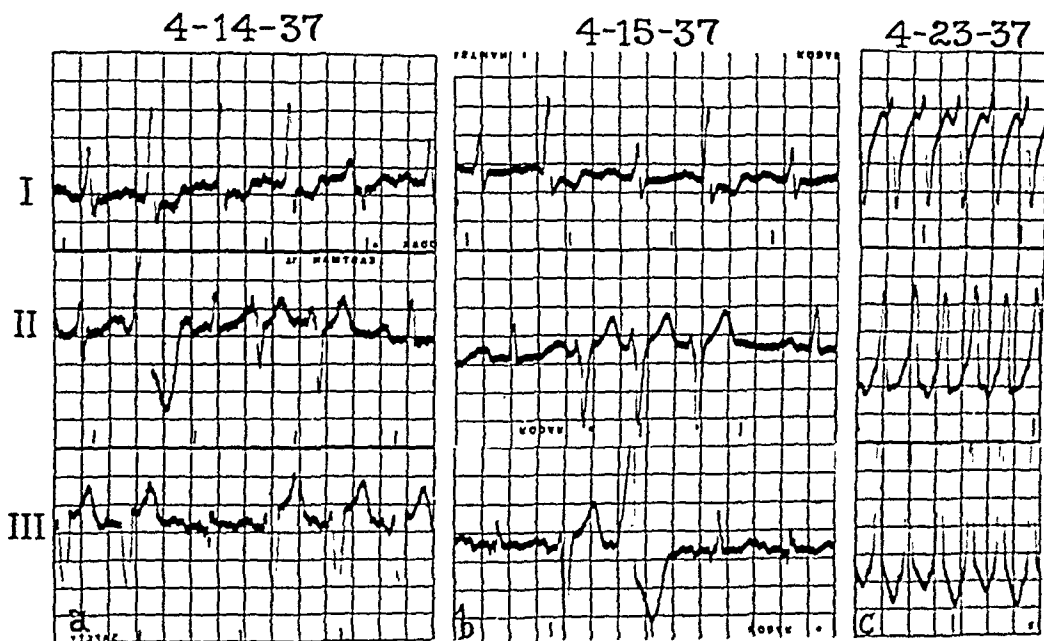


Fig. 7.—Series of electrocardiograms made at varying intervals after an acute attack of coronary occlusion; a, on April 14, 1937, several days after the acute attack had occurred, the normal beats were followed by a series of four or five ventricular extrasystoles from multiple foci; b, on April 15, 1937, one ventricular extrasystole occurred for each normal beat, as well as frequent short series of ventricular extrasystoles from multiple foci; c, on April 23, 1937, several hours before the death of the patient, ventricular tachycardia was present, with a rate of 254 beats per minute.

Fig. 6a, b, c, d, e, and f is a series of electrocardiograms which were made after acute coronary occlusion in one of the cases in this series. The one (Fig. 6a) made March 19, 1937, revealed one ventricular extrasystole in every four beats, slight elevation of the S-T segment in Lead I, and a depressed S-T segment in Leads II and III. In the tracing (Fig. 6b) made on the next day, definite inversion of the T wave in Lead I

appeared, but only one ventricular extrasystole was visible in the entire record. The electrocardiogram (Fig. 6c) made March 22, 1937, showed that the ventricular extrasystoles had become very frequent again; they were occurring once in every five beats. The ventricular extrasystoles were still frequent on March 24 (Fig. 6d), but were completely absent in the tracing (Fig. 6e) made March 27, 1937. Frequent extrasystoles and short runs of ventricular tachycardia were present in the tracing (Fig. 6f) made March 29, 1937. The patient died March 30, 1937, possibly from ventricular fibrillation.

Fig. 7a, b, and c shows the electrocardiograms which were made on another of the patients who died after an acute attack of coronary occlusion. The first tracing (Fig. 7a) was made April 14, 1937, several days after the cardiac accident had occurred, and it shows that one normal beat was followed by a series of four or five ventricular extrasystoles which arose from multiple foci. The next day (Fig. 7b) there was one ventricular extrasystole for every normal beat, as well as frequent, short series of extrasystoles originating from multiple foci. The electrocardiogram (Fig. 7c) made April 27, 1937, several hours before this patient died, revealed that the very frequent ventricular extrasystoles which had been present previously had led to ventricular tachycardia, with a rate of 254 beats per minute. It is possible that ventricular fibrillation supervened and caused the patient's death.

PATHOLOGIC DATA

Since the object of this paper is, as previously stated, to evaluate the factors which influence immediate mortality after acute coronary occlusion it was deemed advisable to ascertain the type of pathologic process and the manner in which death occurred in each of the sixty patients who died within the immediate period. Post-mortem examination of forty-eight of these sixty patients was carried out, and, in the case of the remaining twelve who died, all of the factors which were present were considered in an effort to ascertain the exact sequence of the pathologic events which caused death. It is to be stressed, first, that every patient in this group of sixty had acute coronary occlusion. Table V shows the observations which were made in this particular part of the study. Thirteen of the sixty patients died during the acute attack. These patients had very definite acute coronary artery occlusion, and some of them also had acute myocardial infarction. Three of these thirteen patients had had an attack of coronary occlusion several days before and died while they were suffering from a second attack. Since nothing else was found at necropsy to account for death, and since these patients died during an acute attack, it seems necessary to assume that some abnormality of the cardiac rhythm was the cause. In the light of the previous evidence, we believe that this abnormal cardiac mechanism was ventricular fibrillation. In nineteen other patients nothing

was found at necropsy except acute coronary occlusion and acute myocardial infarction. Clinically, however, nine of these patients had exhibited very frequent ventricular premature contractions, and these had become progressively more frequent until ventricular tachycardia developed among some of them. It is logical to suspect that frequent ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation are likely to be sequential phenomena under these circumstances. It is difficult to explain the cause of the deaths of the remaining ten of these nineteen patients, unless some serious cardiac arrhythmia is assumed to have been present, such as ventricular fibrillation of the type described by Wiggers.

TABLE V
PROBABLE CAUSES OF DEATH IN 60 CASES OF ACUTE CORONARY OCCLUSION

Death during the acute attack (ventricular fibrillation?)	13
Death after the acute attack (ventricular fibrillation?)	19
Myocardial decompensation with gradual failure:	
Pulmonary congestion	10
Pulmonary and hepatic congestion	5
Cerebral thrombosis	4
Massive fatal pulmonary embolism	6
Rupture of the heart with cardiac tamponade	2
Complete auriculoventricular dissociation	1

Evidence of cardiac enlargement in a patient suffering from acute coronary occlusion is believed to be an unfavorable prognostic sign. Necropsy revealed definite enlargement of forty-five of the forty-eight hearts which were examined. At the time of necropsy the estimated average normal weight of the forty-eight hearts was calculated to be 330 Gm.; actually, their average weight was 496 Gm. One heart weighed 720 Gm., and only three weighed less than the estimated normal.

Fifteen of the sixty patients who died within the immediate period gave definite evidence, both clinically and pathologically, of severe myocardial failure after the onset of the acute coronary occlusion and myocardial infarction. Ten of these patients had marked pulmonary congestion (Table V). Examination at necropsy revealed marked chronic passive congestion of the lungs. The other five patients displayed both clinical and pathologic evidence of pulmonary and hepatic congestion (Table V). In addition to the pulmonary observations, it was noted clinically that there was rapid and progressive hepatic enlargement, which, at necropsy, was revealed to be extensive, acute (and, in some cases, chronic) passive congestion of the liver. The average weight of the livers of these five patients was 2,400 Gm., as compared with the average normal of 1,800 Gm. These five patients also had extensive degrees of infarction of the interventricular septum.

Cerebral thrombosis, after which the patient failed rapidly, was present in four instances and was considered to be the cause of death in each of these cases (Table V).

Massive pulmonary embolism, with extensive pulmonary infarction, was noted, and considered to be the cause of death, in six of the sixty patients who died within the immediate period (Table V). Interestingly enough, the site of the thrombus from which the pulmonary emboli originated was not the heart, but one or both iliac vessels.

Rupture of the heart, with cardiac tamponade, was demonstrated at necropsy in two patients (Table V).

One patient had complete auriculoventricular dissociation, and he died during an Adams-Stokes attack which occurred within the immediate period after the acute coronary occlusion.

COMMENT

Of the factors which influence the immediate mortality after acute coronary occlusion, age is the most important. The incidence of acute coronary occlusion in this series was greatest among patients who were 55 years old. However, although 62.5 per cent of the 128 patients in this series had had acute coronary occlusion before the age of 60 years, the incidence of immediate mortality in this group was only 36.2 per cent. The remaining 37.5 per cent of the patients had acute coronary occlusion after they had reached the age of 60 years, and the incidence of immediate mortality in this particular group was 64.5 per cent. It is readily seen that the immediate mortality rate is approximately twice as high among patients who are attacked by acute coronary occlusion after the age of 60 years as it is among those who are attacked before the age of 60 years.

Males in this series predominated by a ratio of 5.4 to 1, but the incidence of immediate mortality for the males was only 41.7 per cent, as contrasted to that of 75 per cent for the females (Table II). This is explained by the fact that 65 per cent of the females in the series were 60 years of age or older, whereas only 32.5 per cent of the males in the entire series were 60 years old or more.

Another of the important factors which influence the immediate mortality rate is the onset of myocardial failure after acute coronary occlusion (Table V).

Evidence is presented to suggest that ventricular fibrillation, either immediate or delayed, probably is another important factor which influences immediate mortality after acute coronary occlusion. Wiggers² has shown that ventricular fibrillation may occur immediately during an acute attack of coronary occlusion, or its appearance may be delayed for a period of several days or weeks. Levy¹¹ has shown that attacks of ventricular fibrillation, terminating in death, have been observed frequently, and Robinson and Bredeck¹² have added that, once the ventricles fibrillate, they rarely recover normal rhythm. Fromet⁸ has shown that ventricular tachycardia is the link which connects ventricular extrasystoles with ventricular fibrillation. Numerous other observers, among whom are Lisa, MacWilliam, and Mahaim,¹³ are of the opinion that an

acutely damaged myocardium is hyperirritable, and that the infarcted portions may be the foci of ectopic beats which, by their summation, lead to ventricular fibrillation. There are certain observations which lead us to assume that this sequence of events occurred in a number of the cases in the present series. In thirteen cases sudden cardiac death occurred during the acute attack itself. Such deaths are difficult to explain, except as the result of a disturbance of rhythm, such as ventricular fibrillation. Nineteen other patients who died within the immediate period may have died of ventricular fibrillation which was delayed in onset. Nine of these patients had electrocardiographic evidence of very frequent ventricular extrasystoles, which then recurred with increasing frequency. In one case a long period of ventricular tachycardia occurred, and the patient died a short time later. It is possible that short periods of ventricular tachycardia might have been found among the remaining eight patients if electrocardiograms had been made at more frequent intervals.

These observations lead us to believe that ventricular fibrillation is foreshadowed by a certain sequence of events. Specifically, our observations suggest that ventricular extrasystoles, when frequent, are very likely to be followed by ventricular tachycardia, and not infrequently by ventricular fibrillation.

Massive pulmonary embolism was the immediate cause of death in 10 per cent of all the patients in this series who died within the immediate period. The source of these pulmonary emboli was not the heart, but the iliac vessels. The convalescent period which follows acute coronary occlusion is ideal for the formation of iliac thrombi because of the decrease in blood pressure after the acute attack and the complete rest in bed and inactivity of the patient.

Using the electrocardiogram to localize the position of the infarct, we found that the incidence of immediate mortality when anterior apical and posterior basal infarcts are present was exactly the same, but the incidence of immediate mortality in the cases in which the position of the infarct could not be localized was twice as high as it was in the cases in which the electrocardiogram clearly indicated the location of the infarct.

SUMMARY AND CONCLUSIONS

One hundred twenty-eight patients who had acute coronary occlusion were studied in an attempt to ascertain the factors which caused sixty of the 128 patients to die within a period of six weeks, while the remaining sixty-eight patients survived the immediate period.

The average age of all the patients in this series was 55 years, and the average age of the patients who survived was 51.3 years, as compared with an average age of 59.2 years for those patients who died within the immediate period. The incidence of immediate mortality among those patients who had acute coronary occlusion after the age of

60 years was approximately twice as high as that among the patients who had acute coronary occlusion before the age of 60 years.

In this series the males predominated by a ratio of 5.4 to 1, but the incidence of immediate mortality among the males was only 41.7 per cent, as compared with an incidence of immediate mortality of 75 per cent among the females. This is explained by the fact that most men who have acute coronary occlusion have it before the age of 60 years, whereas most women who are afflicted by acute coronary occlusion have it after the age of 60 years. The incidence of immediate mortality among those patients who had anterior apical infarcts and those who had posterior basal infarcts was exactly the same, 42 per cent. If it was not possible, however, to localize the position of the infarct by the electrocardiographic pattern which it produced, the incidence of immediate mortality was considerably higher, namely, 81.8 per cent.

The appearance of ventricular extrasystoles after acute coronary occlusion is an unfavorable sign, for these ectopic beats, if they occur very often, apparently have a tendency to increase in frequency until ventricular tachycardia is produced, and this may be followed, in turn, by ventricular fibrillation and death. Once they occur after an acute attack of coronary occlusion, these ventricular extrasystoles must be considered as ominous signs, for, although they may fluctuate and may not be seen in the electrocardiogram at times, nevertheless they do reappear with even greater frequency than before, and within a short time may lead to ventricular tachycardia. Electrocardiograms of this sequence of events are presented. Among nine patients in this series, ventricular extrasystoles which became manifest after an acute attack of coronary occlusion had been very frequent at the onset, and in one patient (Fig. 7) these ventricular extrasystoles then recurred with increasing frequency until they precipitated ventricular tachycardia. It is suggested that in such cases ventricular fibrillation may have ultimately caused death, although its actual existence was never demonstrated.

Rapid and progressive myocardial failure immediately followed acute coronary occlusion and caused death within the immediate period in fifteen of the sixty cases. When a large septal infarct is present, as was encountered in five of these fifteen patients, myocardial failure becomes manifest within a relatively short period and progresses very rapidly.

Massive pulmonary emboli occurred among six of the sixty patients who died within the immediate period.

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SKIN TEMPERATURE CHANGES CAUSED BY SMOKING AND OTHER SYMPATHOMIMETIC STIMULI

J. H. WEATHERBY, PH.D.
RICHMOND, VA.

WITHIN relatively recent years there has accumulated an extensive literature concerning the effects of tobacco on the circulatory system. Generally, such phenomena as changes in blood pressure, pulse rate, and the behavior of peripheral blood vessels, as indicated by changes in the temperature of the skin of the extremities, have been taken as qualitative and quantitative criteria of the nature of these effects. Agreement among the various investigators is by no means perfect, particularly with respect to changes in skin temperature. Also, many investigators seem to have overlooked certain physical and physiologic factors in the production of skin temperature changes which may be of crucial importance in so far as they concern interpretation of these changes. The purpose of this investigation is threefold: first, to add further information, either in confirmation of, or in contradiction to, that already reported; second, to report observations not previously mentioned in the literature; and, third, to interpret these data as carefully as possible, with due consideration for the physical and physiologic environment in which the experiments were conducted. Most of the very extensive bibliography on the subject is omitted for the purpose of conserving space.

THE PROBLEM

After observing changes in the temperature of the skin of the extremities, particularly of the magnitude often reported for the toes (occasionally as much as 6° to 7° C.), it is not surprising that deleterious changes in tissues should be ascribed to them. Does not a single cigarette cause vasoconstriction which persists for almost an hour? And if a person smokes at intervals of forty-five minutes or an hour, would not the peripheral vessels remain in a constricted condition throughout virtually the entire waking period? If this is true, how can the tissues of the hands and feet escape injury such as is seen in thromboangiitis obliterans? Here, as in any other examples of inductive reasoning, the truth and accuracy of the conclusion obviously depend on the truth and accuracy of the premises on which it is based. In this connection it may be well to ask several additional questions. Are the conditions

From the Department of Physiology and Pharmacology, Medical College of Virginia, Richmond.

Received for publication Jan. 22, 1942.

under which temperature measurements are made in the laboratory or hospital comparable to those which exist while the subject is engaged in his usual, daily activities? If vasoconstriction occurs routinely after smoking, is it sufficiently intense to interfere seriously with vital processes in the tissues involved? Are people in general subject to other vasoconstrictor influences which are comparable in frequency and magnitude to smoking? The proper evaluation of the vasoconstriction produced by smoking as an etiologic or influencing factor in peripheral vascular diseases must depend in a large measure on the answers to these questions. Also, the value of skin temperature measurements as a diagnostic aid, and in following the course of such diseases, depends on a full understanding of the factors involved in the regulation of the temperature of the skin of the extremities.

It is obvious that the conditions under which one lives and does his habitual smoking are not comparable to those which generally exist when skin temperature studies are being made in the laboratory. Some investigators, recognizing the necessity for controlling all factors and conditions as completely as possible, have conducted their experiments during the morning hours, with their subjects in the basal metabolic state. This practice assures greater uniformity in the metabolic activities of their various subjects, but it must be admitted that in the ordinary course of events the frequency with which anybody smokes with his body in the basal state is exceedingly limited.

Practically no information has been found in the literature concerning the question whether or not the intensity of the vasoconstriction, as indicated by a fall in temperature, is sufficient to interfere with normal processes in the tissues involved. This question, among others, appears to be answered, at least in part, by experiments to be described later.

The third question, concerning other vasoconstrictor influences to which people in general are subjected during the ordinary course of events, has already been answered in part. Smithwick¹ reports a decrease in blood flow through the finger after a deep breath, immersion of the contralateral hand in cold water, a loud noise, or an unpleasant thought. Similar results are reported by Finesinger, Heusner, and Smithwick.² Mulinos and Shulman³ observed a decrease in skin temperature after a deep breath, such as the inhalation of tobacco smoke, and state that the vasoconstriction is exaggerated by an irritating or painful stimulus which may accompany or shortly follow the deep breath. Also, many investigators comment on the necessity of maintaining quiet during the course of the temperature measurements in order that unnecessarily great fluctuations in temperature may be avoided. Although these various types of stimuli undoubtedly produce peripheral vasoconstriction and a fall in the skin temperature of the extremities, apparently few authors, in reporting such phenomena, have made a direct comparison between the extent of the constriction which they produce and that caused by smoking. In the final analysis, these various

The group of subjects for these experiments consisted of eight women and sixteen men. Four of the women and two of the men were non-smokers. All were normal, healthy persons whose ages varied between 24 and 40 years. With one exception, all were medical students, instructors, or other laboratory workers, so that their participation as subjects probably gave rise to minimum psychic changes. Generally, about four experiments were performed on each subject, although as many as eight or ten were performed on several.

All subjects were comfortably clothed, with only the face, feet, hands, and one arm exposed. With women subjects the regular clothing was supplemented with a blanket over the legs to decrease heat loss from their bare surfaces. Each subject lay on a cot for twenty to thirty minutes before the beginning of observations, or until the temperature of the fingers and toes became relatively constant at a level above 30° C. All refrained from smoking for one or two hours before the experiment. Longer periods of abstinence did not seem to alter the results materially. As a matter of fact, skin temperatures in the morning, eight to ten hours after the last smoke, frequently were lower than those in the afternoon, only one hour after the last smoke. Skin temperatures were measured by means of a thermopile attached to a suitable galvanometer.* These measurements were made at five-minute intervals on the dorsal and palmar surfaces of the third finger near the distal end, and on the dorsal and plantar surfaces of the great toe. Simultaneous records of systolic and diastolic blood pressures and pulse rates were made. In many of the experiments on male subjects, kymographic records of respiratory movements were made during the entire period of observation by means of apparatus similar to that described by Greene and Coggeshall.⁵

EXPERIMENTAL RESULTS

Effects of Smoking.—Under the conditions described above, the smoking of a cigarette (with inhalation) by one accustomed to their use results in the following changes: the systolic blood pressure is elevated 10 to 25 mm. Hg in most subjects, although occasionally, in those who appear to be hypersusceptible, it may be more; the diastolic blood pressure is increased to approximately the same extent, although in some instances the increase is greater in proportion, which results in a decreased pulse pressure; the pulse rate is increased 5 to 20 beats per minute, although again in the hypersusceptible subject the increase may be as much as 30 beats per minute, or even more; the skin temperature of the finger drops 2° to 5° C.; and the skin temperature of the toe drops 3° to 7° C. These changes persist for various periods of time in different subjects, and in the same subject at different times. Usually the time required for recovery is roughly proportional to the magnitude of the change, and varies from fifteen minutes to as much as forty or

*Tycos Dermatherm, manufactured by the Taylor Instrument Co.

showed the greatest rates of change in temperature. It is interesting that neither theoretical curve is based on a temperature change after smoking, but after some other form of stimulation. Fig. 1 shows such theoretical cooling curves, constructed from data obtained from the palmar surface of the finger and the plantar surface of the toe of one

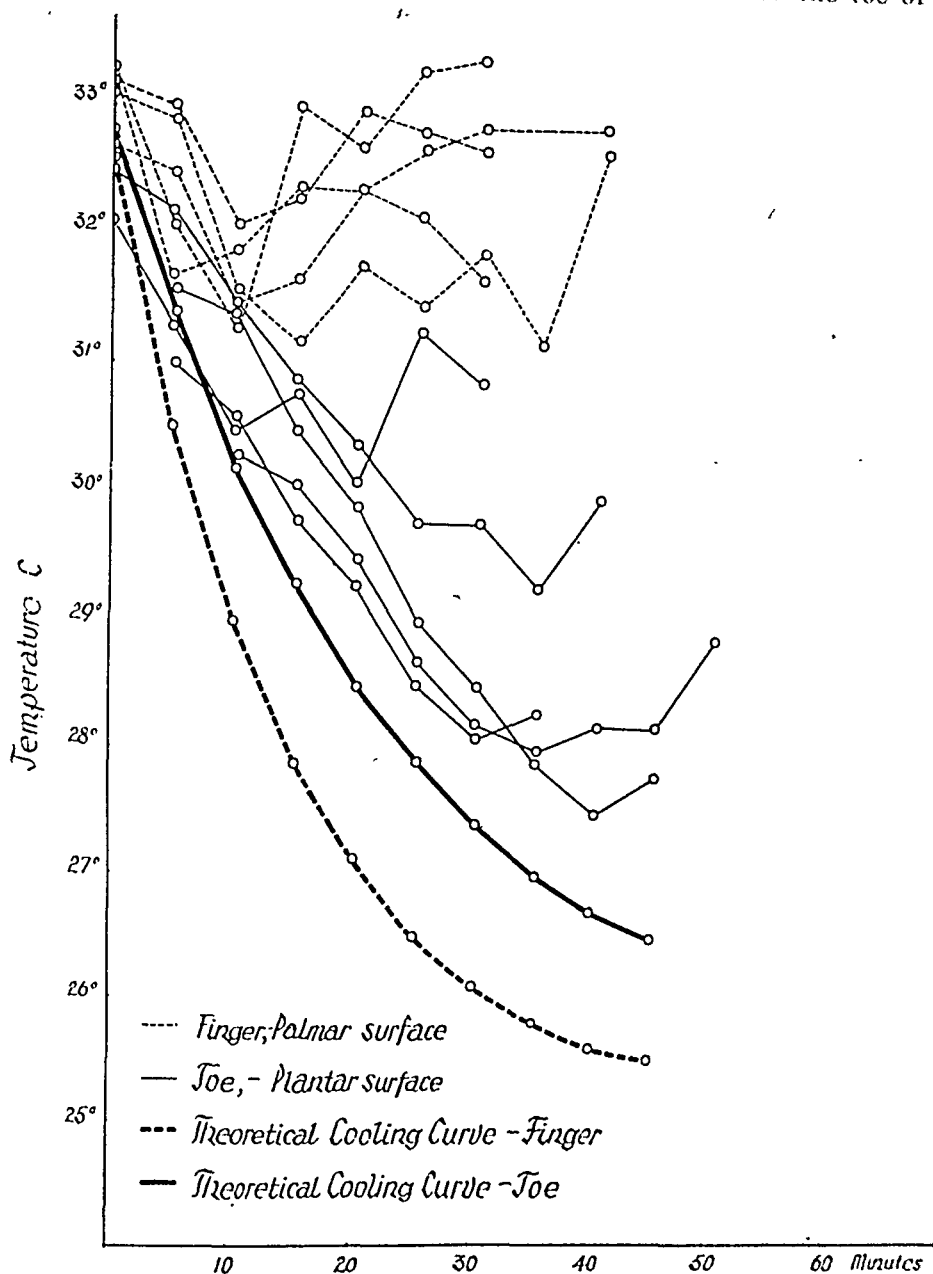


FIG. 1.

subject, as well as actual temperature curves for the same surfaces after smoking cigarettes. It follows, then, that any curve constructed from observed temperatures which does not show a rate of cooling as great as the maximum indicates that vasoconstriction was not complete, and that blood was still flowing through the tissues, although at a reduced

rate. Comparison of the actual temperature curves with the theoretical curves indicates that maximal vasoconstriction may not occur at all, or that it may occur with a duration of ten to thirty-five minutes. Then the flow of blood through the tissues is re-established, or increased if it had never been shut off completely, and the temperature curve follows a course appreciably above that of the theoretical curve for that person.

Effect of High Atmospheric Temperature on Vasoconstriction After Smoking.—Since environmental temperatures of 28°C ., or higher, were found by Sheard, Roth, and Horton⁴ to cause active vasodilatation, the question arises whether or not this dilatation is sufficient to overcome the constrictor influence of smoking. Several experiments were performed with this question in mind. The room temperature was increased to 29° - 30°C . The temperature of the extremities under these conditions was increased to 34° - 35°C . for the fingers, and 33° - 34°C . for the toes. This provided a temperature differential of 4° to 6° , to which may be added an additional degree or two because of the cooling effect of the evaporation of moisture from the surface of the skin. That is to say, in the event of complete vasoconstriction, the temperature of the skin could have been decreased by as much as 6° or 7° . Actually, under these conditions, the temperature of the finger fell only about one-half degree, and that of the great toe, less than one and one-half degrees, after smoking. Within ten to fifteen minutes after cessation of smoking the temperature of both finger and toe was back to the presmoking level. A second cigarette, forty-five minutes after the first, caused no greater change than the first. This experiment was performed on two habitual smokers, each of whom consistently shows a fall of four or five degrees or more when room temperature is maintained at 25°C . It is evident, therefore, that the positive vasodilator stimulus provided by a room temperature of 29° to 30°C . was sufficient to inhibit almost completely the vasoconstrictor influence of smoking. Systolic and diastolic blood pressures and pulse rates were elevated to approximately the same extent as in other experiments on the same subjects at the lower room temperature.

Effect of Smoking on the Rate of Warming.—That smoking provides a relatively weak vasomotor stimulus is indicated further by the following experiments on three male subjects. The room temperature was maintained at 29° to 30°C ., as in the previous experiments. The subjects immersed their feet in water at 15°C . for a period of five minutes. Beginning five minutes after removal of the feet from the cold bath, temperature observations were made at five-minute intervals at several places on the surface of the feet. This was repeated, so that two groups of control observations were obtained on each subject. From this it was found that ten to thirty minutes were required for the skin temperature to regain its normal level under these conditions. The experiment was repeated again, except that the subject began smoking a cigarette about

two minutes after removal of the feet from the cold bath. Under the influence of smoking (with inhalation), approximately one hour was required for the temperature of the feet to regain the normal level in two of the subjects. The third subject in this group did not inhale, as did the others, with the result that normal temperature levels were re-established within twenty minutes. However, the ingestion of 175 c.c. of cold water (15° C.) by this third subject immediately after removal of the feet from the cold bath resulted in such a decrease in rate of warming that thirty minutes were required for re-establishment of normal temperature levels (control period, ten minutes for this subject).

Effect of Removal of Nicotine.—Several experiments were performed in which the subject smoked so-called “denicotinized” cigarettes of a brand available commercially. The effects on skin temperature and circulatory system were not significantly different from those obtained with ordinary cigarettes. The subject used in these experiments is considered to be a hyper-reactor, at least with respect to tobacco. This lack of a significant difference may be explained in at least two ways: first, the changes usually observed after smoking an ordinary cigarette are not caused by nicotine, but by some other constituent; and second, that although nicotine is the agent responsible, maximal effects may be produced by quantities far less than those contained in ordinary brands, and that there still remains in the so-called “denicotinized” brand sufficient nicotine to produce approximately maximal effects. Analyses of the brand used indicate a nicotine content of a little less than 1 per cent.

In order to evaluate the role of nicotine in the production of the characteristic changes in circulation and skin temperature after smoking, the nicotine was removed completely from cigarettes of a popular brand by subjecting them to steam distillation for a period of eight hours. The addition of a small amount of ammonia to the steam apparently resulted in the quantitative replacement of nicotine in the tobacco by ammonia, so that the final acid-base balance of the cigarette was not materially altered. Chemical analyses indicated that the nicotine content was so low as to be practically undetectable. To some of these nicotine-free cigarettes the original nicotine content was restored by injecting a solution of nicotine acetate from a hypodermic syringe. This was done by inserting a long needle through the end of the cigarette and depositing 0.01 c.c. of solution of the proper concentration at intervals of 5 mm.

The effects on blood pressure, pulse rate, and skin temperature of smoking one of these nicotine-free cigarettes (with inhalation) by an habitual smoker were similar in most respects to the effects of an ordinary cigarette when the smoke was *not inhaled*; that is, the blood pressure and pulse rate showed no significant change, and the skin temperature fell only a degree, or slightly more, at most. Occasionally the

skin temperature, particularly of the fingers, was elevated instead of depressed. On the other hand, smoking a renicotinized cigarette by an habitual smoker (with inhalation) produced changes like those produced by the original cigarette (Fig. 2). It is difficult to estimate whether or not the effects of the renicotinized cigarette were quantitatively the same as those of the normal, untreated cigarette, for each subject shows considerable variation in his responses from day to day. However, in these subjects, the effects of the renicotinized cigarette were within the range of variability previously observed for each subject. The marked difference between the effects produced by the nicotine-free cigarette and that to which the nicotine had been restored indicates that the changes in blood pressure, pulse rate, and temperature of the skin of the extremities are caused, for the most part, by the nicotine contained in the latter, and not by altered respiratory movements associated with smoking, as suggested by Mulinos and Shulman.³

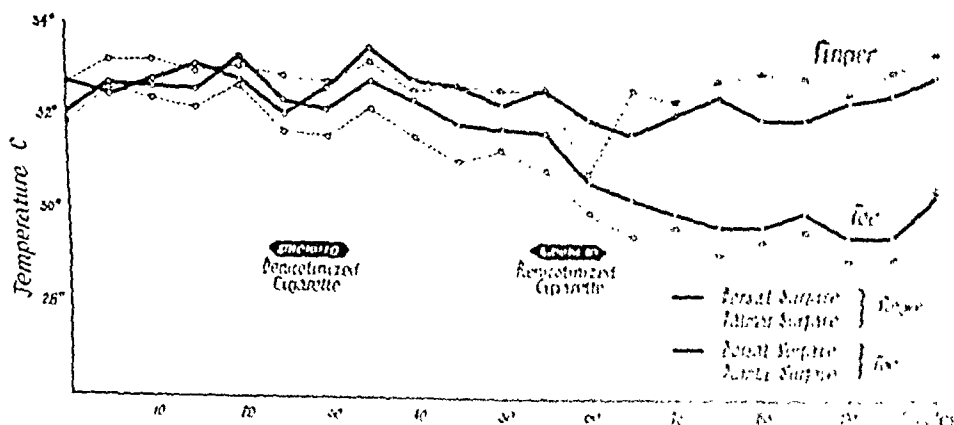


FIG. 2.

Effect of Altered Respiratory Movements During Smoking.—Further evidence that the altered respiratory movements associated with smoking were of relatively little importance in bringing about the fall in skin temperature was obtained from kymographic records of the respiration of many subjects (both smokers and nonsmokers) before, during, and after smoking. The changes appeared to be quite inconsistent. In some nonsmokers, respiratory exchange seemed somewhat depressed during smoking. Some habitual smokers showed relatively slight irregularity during the smoking period, as compared with the pre- and post-smoking periods, whereas others showed considerable irregularity, particularly as a result of inhalation. Of special significance is the fact that two subjects who consistently showed nearly equal temperature changes also showed the greatest differences in respiratory records: one was quite regular, and the other was quite irregular.

Effects of Other Physiologic and Psychic Stimuli.—At frequent intervals throughout the course of the experiments on smoking it was observed that sudden changes in skin temperature occurred, even before

the subject had begun smoking. These changes often were associated with such incidents as the ringing of the telephone, the opening of a door, or other minor disturbances. Such observations, along with those previously reported in the literature, prompted the investigation of the effects of several physiologic and psychic stimuli on skin temperature. These were hyperventilation, the drinking of cold water, a sudden noise, reading, and talking. The hyperventilation consisted of breathing at approximately twice the normal depth for a period of one minute. Usually about ten such breaths were taken during the course of one minute. The cold water was at a temperature of about 12° C., and each subject drank about 150 to 175 c.c. Sudden noises were produced by crushing an inflated paper bag, dropping the lid upon a metal box, or slamming a door. Apparently, any form of reading matter, science or fiction, served equally well, and pictures were found to have a similar effect. Conversation, regardless of subject, was generally effective, although subjects of immediate or personal interest produced greater effects. All these types of stimuli caused a significant fall in skin temperature of a magnitude which often approached or even exceeded that observed after smoking (Fig. 3). Occasionally there was what appeared to be a spontaneous fall in temperature which could not be associated with any known stimulus. The magnitude of the changes brought about by these different activities varied between wide extremes, which makes an arithmetic average fall in temperature, or an average increase in systolic blood pressure or pulse rate, of questionable significance. The important feature in this connection is that every habitual smoker, with the possible exception of two hypersusceptible subjects, exhibited changes after one or more of these physiologic or psychic stimuli which often were as great as those observed after smoking.

Additive Effects.—Not infrequently it was observed that the effects of one stimulus were superimposed on those of another which had occurred earlier, as mentioned by Mulinos and Shulman.³ As an example, occasionally the telephone rang, or someone entered the laboratory shortly after the temperature curve after smoking had reached a minimum level and had begun to ascend, resulting in a resumption of the downward trend of the curve (Fig. 3).

Effect of Smoking on the Active Subject.—All the experiments described above were performed on subjects who were lying down, with their feet and hands exposed, and provide little information which can be applied to those who are wearing the usual foot coverings and are moving about performing their routine duties. For the purpose of obtaining information about temperature changes under the more normal conditions, an iron-constantan thermocouple was sewed into the toe of a sock in such a position that it was in contact with the skin of the plantar surface of the great toe. The shoe was then replaced. The thermocouple was attached to a recording thermometer* by means of

*Celectray, manufactured by the C. J. Tagliabue Co.

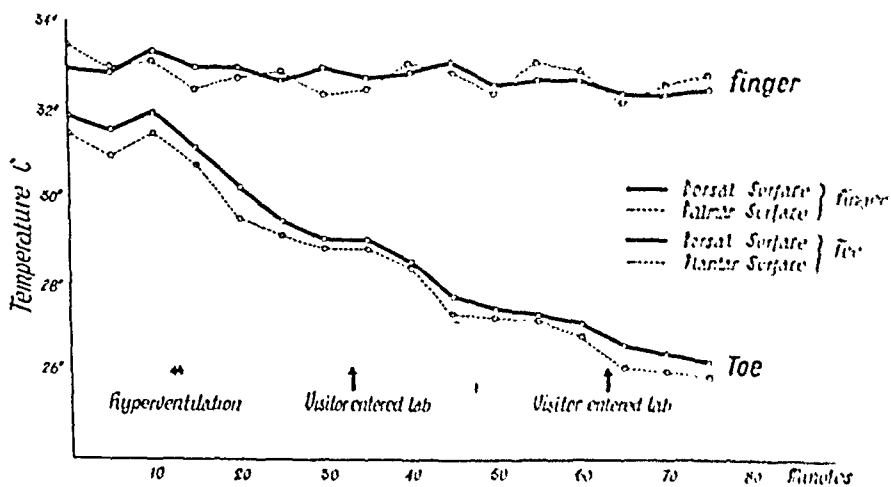
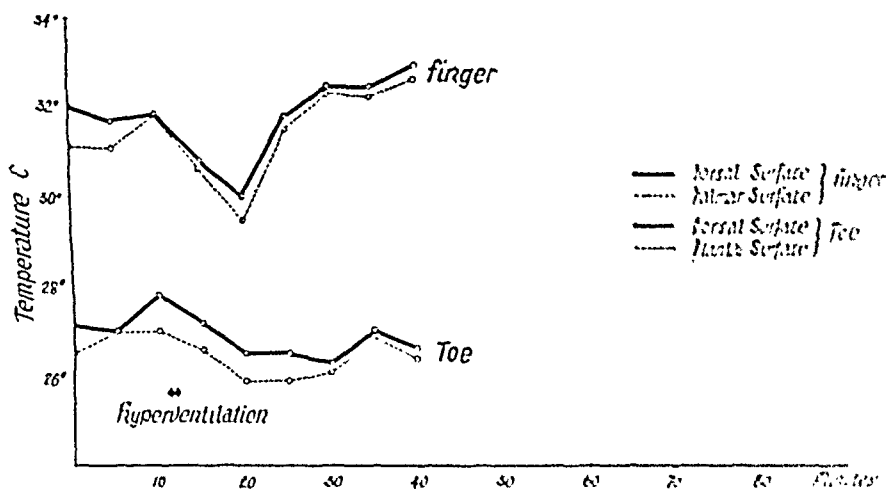
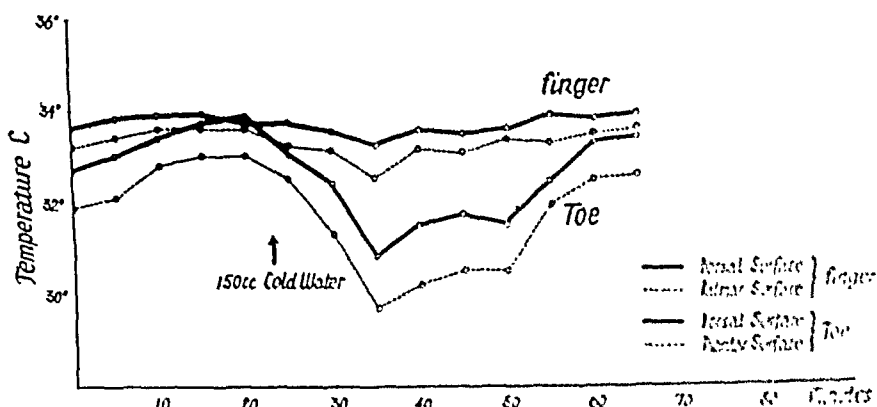


Fig. 3.

wires long enough to allow limited freedom of movement. The subject of this experiment then busied himself with observations on another subject, the recording of data, and similar activities. On smoking a cigarette a maximum fall in temperature of one-half degree from the control level of 30° C. was recorded. A similar experiment on a second subject yielded essentially the same result. Even though the room temperature was 25° C., the temperature within the shoe was high enough to prevent to a great extent the vasoconstriction caused by smoking, just as in previous experiments in which room temperature was elevated to 30° C.

The skin temperatures of the great toes of two subjects were measured on several successive days immediately after they had returned to the laboratory from lunch. During their absence from the laboratory these subjects spent thirty minutes to an hour walking around outdoors at a temperature of 10° to 12° C., and on one occasion one of the subjects returned with damp shoes and socks because it was raining at the time. Temperature measurements were made as quickly as possible after they entered the laboratory, lest the relatively warm room (25° C.) cause a change. In no instance was the temperature of the great toe found to be less than 30° C., and often it was as high as 33° C. No attempt was made to limit smoking during this period, and on two occasions the subjects were smoking at the time the observations were made. This is not to be interpreted as suggesting that the feet never become chilled when a person spends a considerable period of time outdoors in cold weather. Almost everyone has had experiences to the contrary. However, these observations do indicate that one is frequently able to keep his feet and toes warm and well supplied with blood in spite of smoking and a relatively cool external temperature. Here again one may reasonably assume that the insulation provided by shoes and socks was sufficient to maintain the temperature within the shoes at a level high enough to neutralize the vasoconstrictor effect of smoking, just as was observed in experiments conducted at a room temperature of about 30° C.

From these experiments one may conclude that, during rest and relaxation in the laboratory or hospital, the rate of heat production in the body is so low that there is little or no counteraction against the vasoconstrictor effect of smoking. Once constriction has been produced under these conditions, it may persist for a period of several hours, or until dilatation is caused by the intervention of some other factor, such as an increase in heat production or the more thorough insulation of the body against heat loss. When the rate of heat production is above this low level, as it is when a person is walking or actively engaged otherwise, the necessity for an increase in the rate of dissipation of heat from the body often results in vasodilatation in the feet, even though the atmospheric temperature may be relatively low. Obviously, then, experimental conditions in the laboratory or hospital are not strictly comparable to those under which a person habitually lives.

DISCUSSION

Vasoconstriction in the fingers and toes, regardless of cause, cannot cause a fall in skin temperature to a level much below that of the surrounding atmosphere. If the initial skin temperature is equal to that of the atmosphere, a further decrease from vasoconstriction can hardly be expected. Wright⁷ reports that in four of his subjects whose finger temperatures were equal to atmospheric temperature there was no further decrease on smoking. Maddock and Collier⁸ report a fall of 5.9° C. in the temperature of the fingers and 1.5° C. in that of the toes after three cigarettes were smoked in rapid succession. That there was a relatively slight change in toe temperature in this experiment was probably because the initial temperature was about 0.4° C. below room temperature, which also fell about a degree during the course of the experiment. The significant change in finger temperature is in keeping with the fact that initially it was nearly six degrees above room temperature.

Many authors neglect to state whether or not inhalation was practiced by their subjects; yet the evidence indicates that this is of great importance in interpreting the results. The smoking of nicotine-free cigarettes, as pointed out above, or the passage of the smoke through water or cotton saturated with ferric chloride solution, as described by Maddock and Collier,⁸ suppresses the temperature changes to a marked extent. Also, smoking without inhalation, in nonsmokers, at least, may cause an increase in skin temperature instead of a decrease. Some of the variations in the results which have been reported can probably be ascribed to the fact that some subjects inhaled and others did not.

Apparently, few authors have given more than passing attention to the fact that temperature changes which are often equally as great as those caused by smoking, and not infrequently much more prolonged, are brought about repeatedly during the course of the day by such trivial incidents as drinking a glass of cold water, a sudden noise, reading, or conversation. What, then, is the significance of the fall in skin temperature after smoking? It is difficult to avoid the conclusion that temperature changes, per se, indicate nothing more than sympathomimetic responses, whether they result from smoking or from any one of the various activities of the sort mentioned above which produce comparable changes.

CONCLUSIONS

1. Under most laboratory and hospital conditions the smoking of a cigarette by the average habitual smoker (who inhales) results in the following changes: the systolic blood pressure is increased 10 to 25 mm. Hg; the diastolic blood pressure is increased to approximately the same extent; the pulse rate is increased 5 to 20 beats per minute; and the temperature of the skin of the fingers drops 2° to 5° C., and that of

the toes, 3° to 7° C. Occasionally, greater changes occur in hyper-reactive subjects.

2. The smoking of a cigarette by the average nonsmoker (without inhaling) causes only slight changes at most. Generally these are in the same direction as in the habitual smoker, although not infrequently the skin temperature may increase instead of decrease.

3. A comparison of actual temperature curves obtained after smoking with theoretical cooling curves indicates that maximal vasoconstriction rarely persists for more than a few minutes.

4. An environmental temperature of 30° C. inhibits almost completely the peripheral vasoconstriction caused by smoking.

5. Smoking delays warming of the skin of the feet after a cold foot bath. Drinking cold water has a similar effect.

6. Complete removal of the nicotine from cigarettes abolishes almost completely the changes listed in 1. Restoration of the original nicotine content to such cigarettes restores the original effects, indicating that nicotine is the most important agent which contributes to the circulatory and skin temperature changes.

7. Changes in the nature of the respiratory movements during smoking are not responsible for the fall in skin temperature.

8. Various physiologic and psychic stimuli, such as reading, talking, sudden noises, drinking cold water, and hyperventilation, may cause changes in skin temperature comparable to those produced by smoking.

9. Mild physical activity, even at relatively low atmospheric temperatures, inhibits the fall in skin temperature after smoking.

10. Conditions in the laboratory or hospital under which experiments such as the above usually are performed are not strictly comparable to those under which a person lives and indulges in his habitual smoking. Consequently, the results obtained under the one set of conditions are not applicable to the other set of conditions.

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UNUSUAL ARRHYTHMIAS DUE TO MULTIPLE SITES OF
CONDUCTION DELAY IN THE A-V JUNCTION IN CASES
WITH A SUBSIDIARY VENTRICULAR PACEMAKER
LOCATED ABOVE THE BIFURCATION
OF THE COMMON BUNDLE

R. LANGENDORF, M.D., AND L. N. KATZ, M.D.
CHICAGO, ILL.

THE electrocardiographic diagnosis of impaired A-V conduction is simple if the ventricles are controlled only by the sinus node. A prolonged P-R interval indicates delayed A-V conduction, and the absence of a ventricular complex following a P wave indicates blockage of the sinus impulse on its way to the ventricles. However, the interpretation of the electrocardiogram becomes more difficult as soon as the ventricles respond to a subsidiary pacemaker as well as to the sinus node, whether the second pacemaker is due to the passive escape of a subsidiary pacemaker below the region of A-V block during ventricular pauses, or to the usurpation of control over the ventricles by an overactive subsidiary pacemaker. In such instances depressed conductivity causing A-V block and interference causing A-V dissociation may coexist and result in complex arrhythmias.¹

In this report three cases are presented; two are cases of partial A-V block with A-V dissociation of an unusual and rare type,²⁻⁴ and the third represents an example of block in the A-V junctional tissue above (complete) and below (partial) a ventricular pacemaker which is located above the bifurcation of the common bundle of a type hitherto, as far as we know, unreported.

CASE 1.—In this case (Figs. 1 and 2) the P waves are upright in all the limb leads and inverted or diphasic in CF₂; they are alike in each lead, and the P-P intervals are fairly regular. The P-P interval is equivalent to a rate of 65 to 73. In Lead I it is 73; in Lead II, 68 to 70; in Lead III, 65 to 67; and in Lead CF₂, 67 to 70.

The ventricular complexes, on the other hand, show irregular spacing. With the exception of one beat in Lead I, a ventricular premature systole, all the ventricular complexes in each lead are alike. The irregularity of the ventricular complexes shows a definite periodicity. The longer R-R intervals vary in length.

From the Cardiovascular Department, Michael Reese Hospital, Chicago.
Aided by the A. D. Nast and Emil and Fanny Wedeles Funds for Cardiac Research.
Received for publication Dec. 19, 1941.

The shorter R-R intervals are practically identical in each lead and are equivalent to a rate of 80 in Lead I, 78 in Lead II, and 77 in Leads III and CF_2 . The differences in rate of the ventricles between leads parallel those of the auricles, and both are probably vagal in origin.⁵

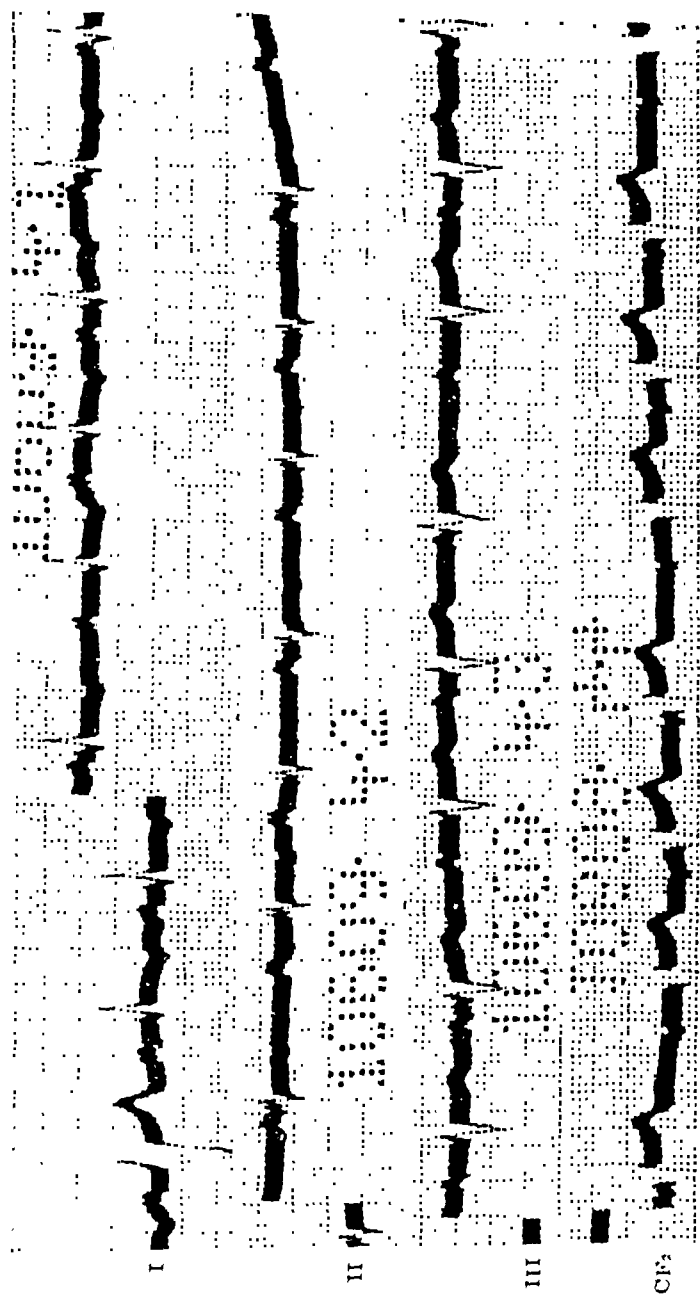


Fig. 1.—Electrocardiogram of Case 1. (The labeling in CF_2 is upside down since the record was taken before the recommendations of the American Heart Association Committee on chest leads was adopted.)

There is no constancy in the relation between P and QRS in this record. The P to QRS time shortens as the short R-R intervals follow each other. When it becomes less than 0.16 sec. (actually 0.10 to 0.16 sec.), a long R-R interval invariably follows.

The presence of regular ventricular activity at a rate higher than the auricular and the progressive shortening of P-R distances at such times indicate that there is a ventricular pacemaker distinct from the sinus node in control of the ventricles, at least at times. In these beats there is apparently interference between

the impulses coming down from the auricle and those traveling toward the auricles from the ventricular pacemaker. The ventricular rhythm arises above the bifurcation of the common bundle and presumably in the A-V node, in spite of a QRS duration of 0.12 sec., since the ventricular complexes in this record are practically identical with those in records taken three days previously and fifteen days later with normal sinus rhythm and prolonged P-R time (Fig. 3).

The occurrence of the longer R-R intervals is ascribed to the absence of discharge of the ventricular pacemaker at the expected time. During these intervals, apparently unlike other cycles, the sinus impulse reaches and discharges this subsidiary pacemaker²⁻⁴ but is itself blocked lower in the A-V junction and fails to stimulate the ventricles. The presence of first degree A-V block in records before and after (Fig. 3) this one would favor the presence of such blockage.

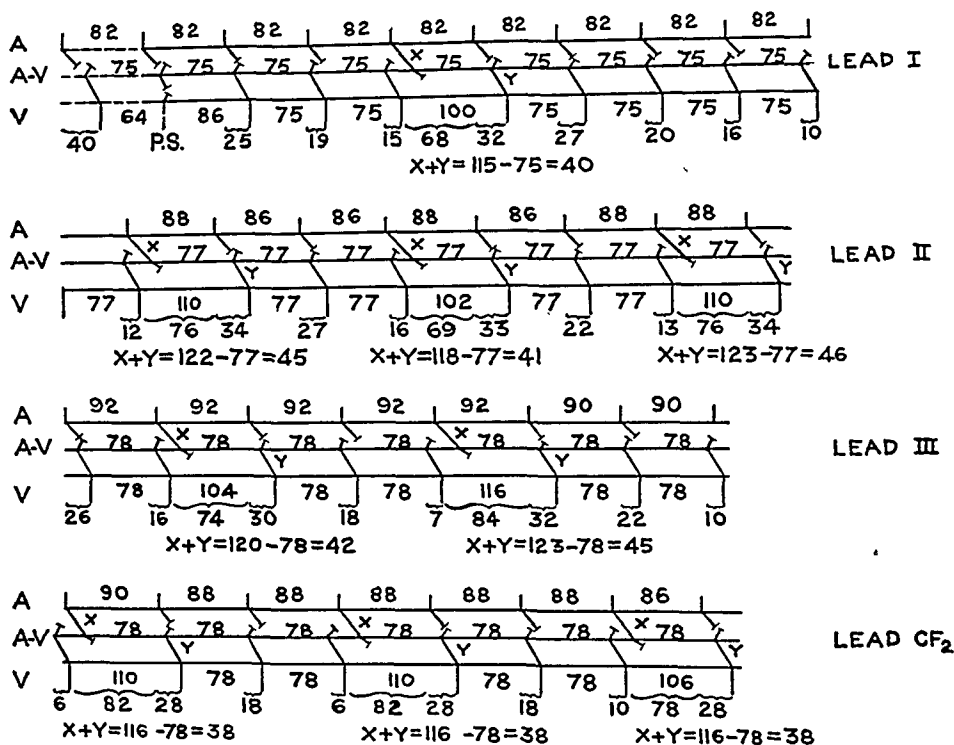


Fig. 2.—Analysis of record shown in Fig. 1. A is the auricular stimulation as marked by the beginning of the P waves; V is the ventricular stimulation as marked by the beginning of QRS; and A-V is the time of discharge of the A-V nodal pacemaker set an arbitrary distance ahead of V. X, Y and X + Y are described in the text. The figures in the lowest line of each lead represent P-R distances (and in the longer pauses R-P distances as well). P.S. is a premature ventricular systole. The values on lines A, A-V, and V give, respectively, the intervals between P waves (P-P interval), the discharge of the ventricular pacemaker, and the intervals between QRS complexes (R-R interval). The time values are in $\frac{1}{100}$ of a second, viz. 99 is 0.99 seconds, etc. Discussed in text.

The nature of the ventricular response which terminates the long pause is not immediately ascertainable. The choice lies between a conducted sinus impulse so that the P-R represents transmission time, or an impulse arising from the ventricular pacemaker reaching the ventricles before the next sinus impulse. We incline to the latter view primarily because the P-R distance of the beats at the end of the long pauses seem to vary directly with the preceding R-P distance rather than as the inverse of the latter which would be the case if the ventricular complexes were due to impulses of sinus origin. Apparently the discharged ventricular pacemaker can rebuild and discharge again before another sinus impulse can reach it.

The R-R distance of the longer pauses varies inversely with the P-R distance of the beat before the pause. This would imply that, as the P-R distance shortens, sinus impulses reach and discharge the ventricular pacemaker later in its cycle. This is also supportive evidence that the ventricular beat after the pause is not sinus in origin.

An idea of the transmission time from the sinus node to the ventricular pacemaker (X) plus that from the latter to the ventricles (Y) can be obtained by subtracting the R-R interval of the shorter ventricular cycles from the time interval between P ahead of the pause to QRS after the pause. We have found no method for determining the relative times of the two components. The values obtained for their sum (X + Y) equal 0.38 to 0.46 sec. and compare reasonably with the P-R intervals found before and after this record was taken (0.50 sec. and 0.36 sec., respectively). However, it has been shown^{6,7} that premature discharge of a ventricular pacemaker may cause a depression of the pacemaker, so that the value assumed for the cycle length of the ventricular pacemaker after its discharge by the sinus impulse may be too short, and hence the value for the conduction times, X + Y, may be too long.

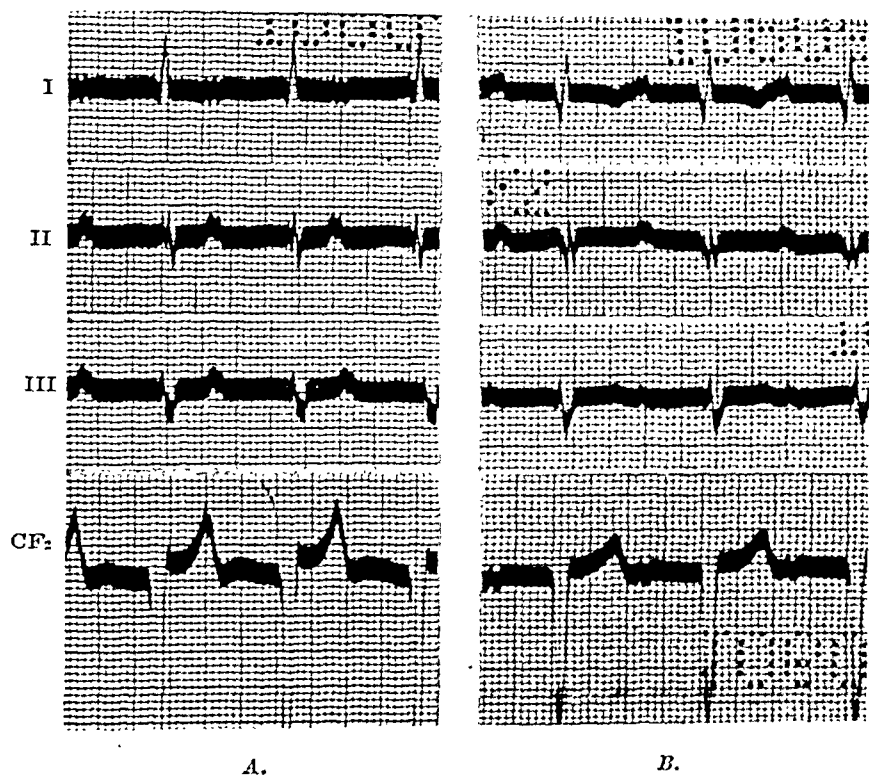


Fig. 3.—Records A and B of Case 1 taken respectively three days before and fifteen days after the record shown in Fig. 1. Discussed in text.

The ventricular premature systole (P.S.) at the beginning of Lead I apparently did not disturb the timing of the ventricular pacemaker, indicating that this premature ectopic impulse did not reach and discharge the regular ventricular pacemaker or that it reached it just when it was due to discharge.

In brief, this is a case of A-V dissociation due to the activity of a subsidiary pacemaker located above the bifurcation of the common bundle, presumably within the A-V node. The rate of this ventricular pacemaker exceeds that of the sinus node. It is associated with a constant retrograde block located somewhere in the A-V junctional tissue above the ventricular pacemaker. In addition, there is evidence of (forward) A-V block, since P waves falling in diastole outside the normal refractory period of the A-V junctional tissue and with sufficient time for

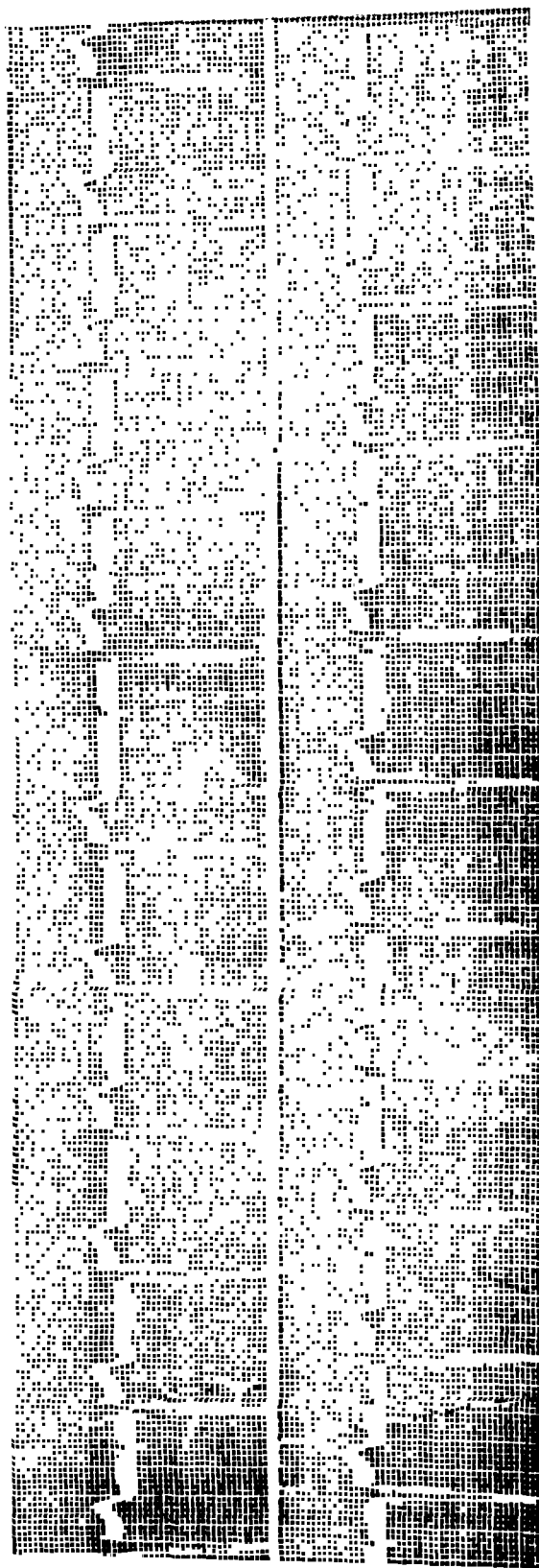


Fig. 4.—A continuous strip of Lead CF₂ of the record of Case 2 analyzed in Fig. 5 and discussed in text.

a P-R of normal duration to occur do not give rise to a ventricular response. Some ventricular beats occur under exceptional conditions and may at first appear to be conducted beats, but on further analysis this seems unlikely.

The unusual phenomenon that distinguishes this case of A-V dissociation from the usual type is the peculiar arrhythmia of the ventricular pacemaker. This is caused by the sinus impulse which sometimes arrives after the absolute refractory phase of the region in the A-V junction above the ventricular pacemaker and discharges the ventricular pacemaker without being conducted through to the ventricles.

Although there is not one ventricular beat resulting from an impulse in the sinus node, there is evidence that conduction is possible along the whole pathway from the sinus node to the ventricular muscle, since conduction occurs in some beats from the sinus node to the site of the ventricular pacemaker and in many other beats from this point to the ventricles. In this case, therefore, there is a permanent retrograde A-V block, complete A-V dissociation, and partial (forward) A-V block. The retrograde block is nearest the auricles, and the complete dissociation occurs below it; both are located above the ventricular pacemaker. The partial (forward) A-V block, however, is located in part between the ventricular pacemaker and the ventricles.

CASE 2.—This case (Figs. 4 and 5) shows essentially the same arrhythmia as Case 1, namely, complete A-V dissociation. The auricles are controlled by the sinus node, and the ventricles, by a ventricular pacemaker located above the bifurcation of the common bundle, presumably in the A-V node. Long ventricular pauses also occur (whenever the P-R distance becomes less than 0.11 sec.). The ventricular pauses are less frequent in this case than in the previous one because there is less difference between the rate of the sinus node and the ventricular pacemaker. Long pauses actually occurred only three times in a record containing 50, 50, 50, and 67 successive cycles in the three limb leads and the one chest lead (the last two are shown in Figs. 4 and 5).

The rate of the sinus node varies from 58 to 68; that of the ventricular pacemaker, from 61 to 68. When the rates of the two pacemakers are almost identical, the relation of P to QRS remains constant for many cycles and superficially suggests a sinus rhythm with 1:1 conduction and a prolonged P-R interval. However, examination of the entire Lead CF₂ record proved conclusively that A-V dissociation is actually present throughout, although becoming more evident whenever the rate of one pacemaker changes without corresponding change in the rate of the other.

The long ventricular pauses in this case occur only when the preceding P to QRS distance is 0.11 sec. or less (0.10; 0.08; 0.11 sec.). The interval from P preceding the long ventricular pause to QRS after the pause is fairly constant measured 1.42, 1.36, and 1.39 sec. The nature of the beat following the long ventricular pause is more difficult to determine than in Case 1. However, for similar reasons,

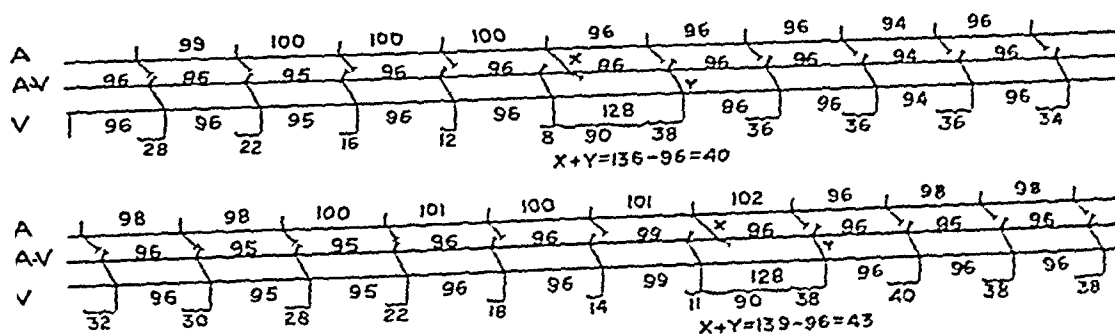


Fig. 5.—Analysis of record shown in Fig. 4. Conventions as in Fig. 2. Discussed in text.

the beats terminating the long-ventricular pauses are probably not due to conducted sinus impulses. The distance from QRS ahead of the pause to the P during the pause was constant in all three pauses (0.90 sec.), and therefore the distance from P during the pause to QRS terminating the ventricular pause would be expected to be constant if this latter were a conducted beat. Actually, the P-R distance after the pause measures 0.41, 0.38, and 0.38 sec. These differences can be explained on the assumption that the beats after the pause are ventricular beats since the longer P-R distance of 0.41 sec. is associated with slowing of the ventricular pacemaker.

The sum of the conduction time from the auricles to the site of the ventricular pacemaker (X) and that from this point to the ventricles (Y) equals 0.42, 0.40, and 0.43 sec., indicating the presence of partial (forward) A-V block.

This, then, is another instance of A-V dissociation with permanent retrograde A-V block, both located above the ventricular pacemaker, and partial (forward) A-V block located somewhere below the ventricular pacemaker. The latter occurs on these occasions when the sinus impulse discharges the ventricular pacemaker and fails to reach the ventricles.

CASE 3.—This record was taken on a "digitalized" patient, and the effect of the drug is reflected in the contour of the S-T-T complex (Fig. 6). No P waves are seen in any of the three leads; instead, there are fine oscillations of the base line indicating fibrillation of the auricles.

The ventricular complexes are of the supraventricular type and show irregular spacing. However, as shown in Table I, all but two of the R-R intervals fall into one of two groups; they are either short (0.84 to 0.88 sec.) corresponding to a rate of 68 to 71, or long (1.66 to 1.74 sec.) corresponding to a rate of 35 to 36. Because the long R-R intervals are almost exactly twice as long as the short ones and are fairly constant, it is unlikely that they are due to impulses conducted from the fibrillating auricles to the ventricles. It is more likely that these ventricular beats are responses to a regularly discharging pacemaker located above the bifurcation of the common bundle, presumably the A-V node, which are conducted through a depressed region in the A-V junction which leads, at times, to a dropping out of every other impulse, viz., partial block (intermittent 2:1) between the ventricular pacemaker and the ventricles. This further presupposes the presence of complete A-V block between the auricles and the ventricular pacemaker.

TABLE I
DURATION OF SUCCESSIVE R-R INTERVALS IN 0.01 SEC.

Lead I	88, 85, 85, 84, 85, 84
Lead II	166, 166, 124, 84
Lead III	174, 172, 170, 108

However, there are two R-R intervals, the third in Lead II and the fourth in Lead III, measuring 1.24 and 1.08 sec., respectively, which do not fit into either of the above categories. The length of these intervals can be explained if it is assumed that the block below the ventricular pacemaker is of the type associated with the Wenckebach phenomenon (Fig. 7).

Although we cannot determine the conduction time from the ventricular pacemaker to the ventricles, its duration should be longer when 1:1 conduction is present than when every other beat is blocked. Since the third R-R in Lead II occurs on resumption of 1:1 conduction, the transmission time of the beat before this interval should be considerably shorter than the conduction time of the beat following. Once 1:1 conduction is established, the prolonged conduction time would remain approximately constant and the R-R interval would then correspond

to the cycle length of the ventricular pacemaker. Thus the difference in conduction time from the ventricular pacemaker to the ventricles of the last beat of 2:1 block and that of the next beat is responsible for the lengthening of the transitional R-R interval. The difference between this R-R and that of established 1:1 conduction measures 0.41 sec. in Lead II and presumably would have been 0.21 sec. in Lead III if one assumes that the R-R interval of 1:1 conduction after the transitional R-R interval would have measured half the longest R-R interval. It is regrettable that longer strips of this record were not available.

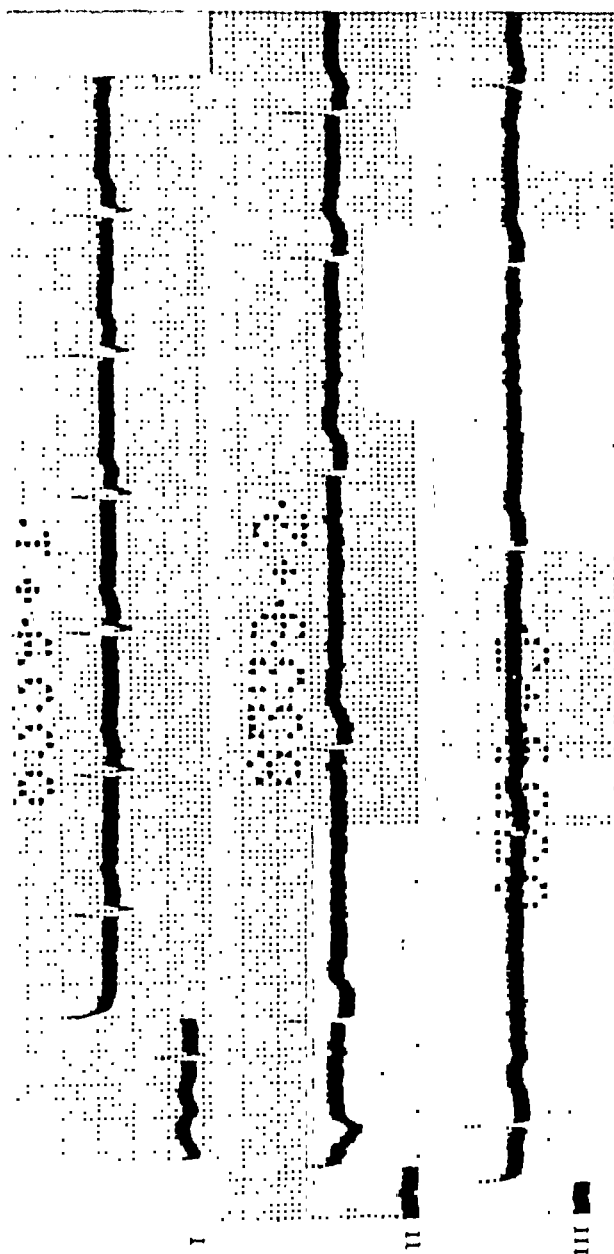
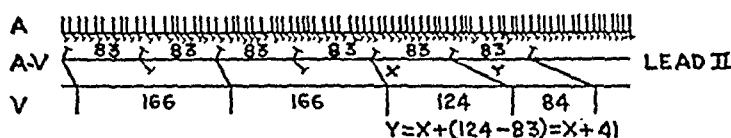


Fig. 6.—Electrocardiogram of Case 3; Lead II of this record is analyzed in Fig. 7. Discussed in text. The record shows "overshooting," but this does not obscure the digitalis effect on the S-T-T.

In brief, this is a case of auricular fibrillation in which digitalis produced a complete A-V block and the ventricles were controlled by a subsidiary pacemaker above the bifurcation of the common bundle, presumably the A-V node. However, the A-V junctional tissue below this pacemaker was also in a depressed state and thus unable to transmit without delay the impulses initiated by the ventricular pacemaker. At times, there was a simple delay in conduction; at other times,

there was a dropping out of every other impulse associated with a shortening of the conduction time of the conducted beats. Because of the changes in conduction time at the transition from 2:1 to 1:1 rhythm an R-R interval appeared that was longer than those after 1:1 conduction was established and exactly like that found in the Wenckebach phenomenon.



lating the ventricles. However, it is evident from the analysis presented that conduction is possible along the whole A-V conduction pathway. The sum of the conduction time from the auricles to the ventricular pacemaker and from this point to the ventricles can be determined and, when measured, indicates delayed A-V conduction.

Case 3 shows auricular fibrillation with complete A-V block above the ventricular pacemaker and partial A-V block with the Wenckebach phenomenon in a region between the ventricular pacemaker and the bifurcation of the common bundle.

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ATHEROMATOSIS OF THE MITRAL VALVE

C. ALEXANDER HELLAUIG, M.D.
WICHITA, KANSAS

A PREVIOUS study¹ of coronary sclerosis in sixty-two autopsy cases led to the following conception of the genesis of atherosclerosis. The earliest lesion is an accumulation of finest lipid granules in the ground substance of the intima. The source of these lipid deposits is the blood plasma which nourishes the intima. The retention of lipid in the intima is favored by a high-cholesterin content of the blood plasma and by a disturbance of the lymph flow in the intima.

The next step in the development of atherosclerosis is the appearance of fat-filled cells which have taken up the lipid from the ground substance. During the ascending period of life accumulation of fat in the intercellular substance and in the cells of the intima is not associated with proliferation of connective tissue, and destructive changes characteristic of advanced atherosclerosis are entirely absent.

In middle life, an extensive fibroplastic process arises in the diseased arteries. Following injury of the tissue by the accumulation of lipid, granulation tissue develops. At first many small blood vessels are present in the young connective tissue. They originate from vasa vasorum of the media, and they may communicate directly with the lumen of the diseased artery. After collagenous fibers have been formed, the vascular tissue loses its blood vessels, and a dense hyaline scar results. This cuts off the lipid deposits from blood and lymph supply, and the fat-laden cells and fibers become necrotic. The space occupied by dead cells is converted into a cavity filled with detritus, cholesterol crystals, and fluid; this is the so-called atheromatous abscess.

If this abscess ruptures into the lumen of the artery, ulceration of the wall and thrombosis may occur. From the lumen of the diseased vessel, blood may invade the intima, causing hematomas in the wall. Calcification of the necrotic area in the intima occurs after the liberation of glycerin and crystalline cholesterol and the formation of insoluble calcium soaps. This completes the picture of atherosclerosis.

The results of my previous study showed that the whole process of atherosclerosis is initiated and governed by deposits of cholesterol in the intima, and that the destructive changes in the diseased vessel depend upon the fibroplastic reaction of the intima. This conception of

From the Department of Pathology, St. Francis Hospital.
Received for publication Dec. 9, 1941.

TABLE I

SUMMARY OF MORPHOLOGIC FINDINGS IN 100 CASES OF ATHEROMATOSIS IN ANTERIOR LEAFLET OF MITRAL VALVE

CASE	SEX	AGE (YR.)	CLINICAL DIAGNOSIS	GROSS LOCALIZATION			MICROSCOPIC FINDINGS	
				MEDI- AL	CEN- TRAL	LATER- AL	FIBRO- ELAS- TIC	MID- DLE PLATE
1	M	2	Bronchopneumonia	+			++	
2	F	2	Bronchopneumonia		+		+	
3	F	3	Little's disease	+			+	
4	M	9	Poliomyelitis		+		++	
5	M	11	Liver rupture		+		++	
6	F	11	Peritonitis	+	+		++	
7	M	14	Rheumatic heart	+		+	++	
8	M	16	Cavernous sinus thrombosis		+		++	
9	M	16	Brain tumor		+			
10	M	19	Lung gunshot	++			+	
11	M	21	Peritonitis	++			++	
12	M	27	Acute myocarditis	++			++	
13	M	24	Encephalitis		+			
14	F	25	Lobar pneumonia	+	+	+		
15	M	30	Ulcerative endocarditis		+			
16	M	35	Appendicitis	+	++	+		
17	M	36	Septic endocarditis	+	+		++	+
18	F	38	Syphilis		++			
19	F	38	Peritonitis		++			
20	M	39	Ulcerative endocarditis	+	++	+		
21	M	38	Coronary occlusion	++	++			
22	M	40	Lung abscess			+	+	+
23	M	40	Influenza pneumonia	+	++	++	++	++
24	M	41	Syphilitic aneurysm			+++	+++	++
25	M	42	Coronary occlusion	+++	++	+		
26	M	44	Strychnine poisoning	+	+++			
27	F	45	Diabetes		+++			
28	F	45	Mitral stenosis	+				
29	M	46	Glomerulonephritis	+	+++			
30	M	46	Coronary occlusion	+++	++			
31	M	47	Coronary occlusion	+	+++	+		
32	M	47	Anesthesia death	+	+++	+		
33	F	47	Carcinoma coli	+	+++	+	+++	++
34	F	48	Carcinoma of cervix	+	++	+	+++	+++
35	M	49	Coronary occlusion	+	+++	++		
36	M	49	Pneumonia, hypertension	++	+++	++	+++	++
37	M	49	Hypertension		+++		++	+++
38	M	50	Arsenic poisoning	++		++	++++	++
39	M	50	Skull fracture	+	++	+		
40	F	50	Rupture of aorta	+	++	+		
41	F	50	Carcinoma of ovary		++		+++	++
42	M	50	Coronary occlusion	+	+++	+	++	++
43	M	52	Heart gunshot	++	++		++	++
44	M	52	Apoplexy		++	+		
45	M	53	Anesthesia death	+	+	+		
46	M	54	Ulcerative endocarditis		++			
47	F	54	Peritonitis	++	++	+	++	+++
48	M	54	Coronary occlusion	++	++	++	++	++
49	F	55	Aortic stenosis	++	++		++	++
50	M	55	Nephrosclerosis	+	++	+	++	+++
51	M	55	Coronary occlusion		+++			
52	M	55	Rupture of aorta		++			
53	F	56	Bronchial asthma	++	+	+	+++	+++
54	F	57	Liver rupture		++	+		

TABLE I—CONT'D

CASE	SEX	AGE (YR.)	CLINICAL DIAGNOSIS	GROSS LOCALIZATION			MICROSCOPIC FINDINGS	
				MEDI- AL	CEN- TRAL	LATER- AL	FIBRO- ELAS- TIC	MID- DLE PLATE
55	M	57	Leucemia	++	+++			
56	F	57	Pneumonia		++			
57	F	57	Pulmonary embolism	+	++	+		
58	M	58	Coronary occlusion		+++			
59	M	60	Dissecting aneurysm	++	++	++		
60	F	60	Perforating stomach ulcer	+++		++	++	++
61	F	60	Streptococcic pyemia	+	+++	+	++	+++
62	F	60	Pulmonary embolism	+	+	+	++	+
63	M	62	Hypertension	+	+++	+		
64	M	62	Coronary occlusion	+	+++	+		
65	M	63	Coronary occlusion	+	++	++	++	++
66	M	63	Diabetes, coronary occlusion	++	+++	++		
67	M	63	Coronary occlusion		++		+++	++
68	M	64	Carcinoma of tongue	+++	+	+++		
69	F	65	Coronary occlusion	++	+++	++		
70	F	65	Rupture of heart	+	+++	+	++	+++
71	M	67	Syphilis of aorta	++	+++	++		
72	M	67	Hypertension	+	++	+	+++	+++
73	M	67	Diabetes	+	+++	++	+++	++
74	M	68	Apoplexy	+	+++	+	++	+++
75	M	68	Liver cirrhosis	+	++	+		
76	F	68	Myocardial infarct	++	+++	++	+++	+++
77	F	68	Oral carcinoma	+	+++	++	++	+++
78	M	69	Ulcerative endocarditis	++	++	++	++	+++
79	F	70	Coronary occlusion	+	++	+	+++	++
80	F	71	Coronary occlusion	+	++	+	+++	++
81	F	71	Intestinal obstruction	+	++	+		
82	M	71	Aortic stenosis	+++	++	+		
83	M	72	Uremia	+	+++	+	++	+++
84	M	74	Bronchopneumonia	++	+++	++	+++	+++
85	M	74	Stomach carcinoma	+	+	+	+++	+
86	F	77	Bronchopneumonia	+	++	+		
87	M	78	Coronary occlusion	+	+	+		
88	M	78	Cholecystitis	++	+++	++	++	+++
89	M	80	Pyonephrosis, diabetes	+	++	+		
90	M	81	Hypertension	+	++			
91	M	81	Bronchopneumonia	++	++	++		
92	F	81	Apoplexy	+	+++	+		
93	M	81	Hypertension	++	++	++	++	+++
94	M	81	Perforation of rectum	++	++	++	+++	+++
95	F	81	Lobar pneumonia	++	++	++	+++	+++
96	M	82	Bronchopneumonia	++	++	++		
97	M	84	Myocardial infarct	++				
98	M	84	Bronchopneumonia	+	+++	+	++	+++
99	M	86	Apoplexy	+++		+	+++	+++
100	M	87	Coronary occlusion	+	+++	+	++	++

the genesis of atherosclerosis conforms with the view held by Aschoff,² Anitschkow,³ and Leary⁴ that imbibition of the intima with cholesterol plays the foremost role in atherosclerosis.

In a colorful monograph,⁵ Winternitz, Thomas, and LeCompte reported their studies on the biology of arteriosclerosis. By clearing arteries with glycerin, these investigators noticed hemorrhages in the intima at the site of predilection of arteriosclerosis. They contended

that the primary cause of atherosclerosis is rupture of vasa vasorum which, in their opinion, are normally present in the intima. Hemorrhagic diathesis, vitamin deficiencies, mechanical, chemical, and bacterial agents are, according to them, responsible for increasing the permeability of the capillary wall and for causing hemorrhages in the intima. If absorption or organization of these intimal hemorrhages is not complete, the residuum remains as a necrotic focus, the so-called atheromatous abscess.

The conclusions by Winternitz and his co-workers were so much at variance with my own observations that I studied the atheromatous process in structures which are generally regarded as devoid of blood vessels, namely, heart valves.

The present paper is based on the examination of the mitral valve in 100 autopsy cases. After the gross findings were noted, frozen and paraffin sections were made from the cusps and the following staining methods were employed: Sudan III and hematoxylin, hematoxylin and eosin, orcein and van Gieson stain.

My youngest subject was 2 years old; the oldest, 87 years. The gross and microscopic findings are listed in Table I.

GROSS APPEARANCE

Without exception, yellow spots were found only on the ventricular side of the anterior leaflet of the mitral valve and never on the auricular surface. The significance of this predilection will be discussed later.

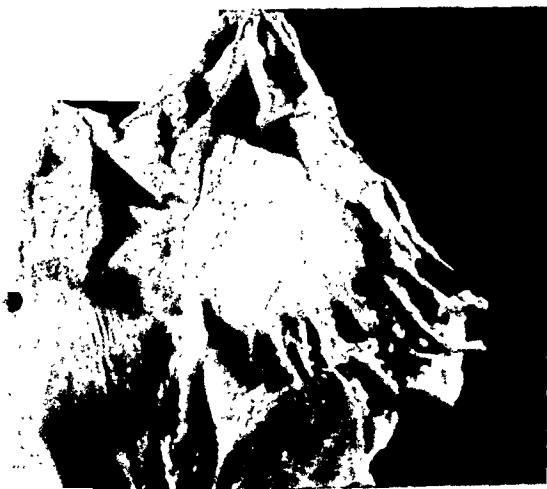


Fig. 1.—Anterior mitral leaflet of a 55-year-old male. Ventricular side with maplike deposits of lipoid.

In early childhood the yellow areas are most often located near the medial and lateral margin of the leaflet. The next most frequent site of lipoidosis is at the insertion of the chordae tendineae. In older people, the chordae themselves are always involved in the process, but again only on the ventricular side. The yellow spots are either completely flat and

within the surface of the valve or slightly raised. Some are sharply defined; others, very indistinct. Their form is round, oval, or irregular maplike. The size varies from 1 mm. to more than 1 cm. At the insertion of the chordae the yellow spots are often triangular, radiating from the cord into the leaflet. In later years, bandlike deposits are found running across the whole leaflet, especially in the upper third. There are often several parallel yellow streaks, between 1 and 3 mm. wide.



Fig. 2.—Anterior mitral leaflet of an 82-year-old male. Bandlike deposits of lipoid on ventricular side.



Fig. 3.—Anterior mitral leaflet of a 71-year-old female. Magnification, $\times 2$. The discontinuity of the lipoid deposits is well shown.

MICROSCOPIC FINDINGS

The normal microscopic structure of the anterior leaflet of the mitral valve has been studied by Sato⁹ and Saltykow,¹⁰ and my own findings are in complete agreement with their description. The leaflet has a fibrous middle plate which is covered on both sides with identical layers. Starting from the ventricular surface the following layers can be dis-

tinguished: (1) the endothelium with the subendothelial connective tissue, (2) the elastic layer, (3) the fibroelastic layer, then the middle plate, and, in reverse order, the fibroelastic layer, the elastic layer, the subendothelial connective tissue, and, finally, the auricular endothelium.

The earliest microscopic alterations are deposits of fine lipid granules in the subendothelial and the fibroelastic layers on the ventricular side of the leaflet. While in many cases fat-laden cells are present at the same time, it can be demonstrated that fatty materials are deposited in the ground substance of the valve before any fat-containing cells are found. The extracellular lipid may be masked by the advent of numerous cells which become laden with fat. At a slightly later stage, the fibroelastic layer contains a considerable accumulation of cells among which large foamy cells resembling xanthoma cells are the most conspicuous. Their outline is rounded or polygonal, sometimes flattened. The nucleus is usually centrally placed, small, round, and deeply staining. In the interstices between the fibers of the fibroelastic layer, there are found other, much smaller, spindle-shaped or stellate cells with round or oval nuclei. Many of the spindle cells contain fatty granules scattered in the protoplasm at either end of the nucleus. These cells are morphologically indistinguishable from fibroblasts.

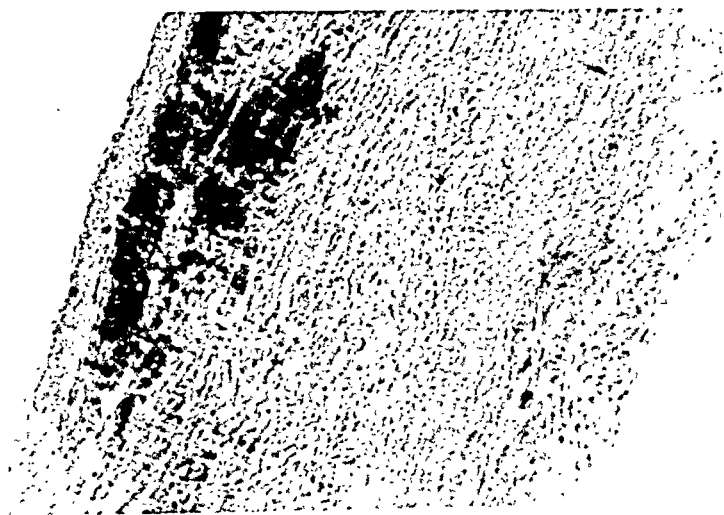


Fig. 4.—Anterior mitral leaflet of a 50-year-old male. Magnification, $\times 50$. The deposits of lipid (dark stained) are found in the ventricular layers only.

After the thirtieth year the amount of lipid deposits increases, and the fatty material extends farther and farther downward from the ventricular side, until, after the age of 40, most of the middle plate is impregnated with lipid. With advancing age, many collagenous fibers of the middle plate appear poorly defined and, when stained with hematoxylin and eosin, small areas of necrosis become evident. Crystals of cholesterolin together with finest granules of calcium accumulate in the necrotic areas. In not a single instance, however, was this process so

extensive that atheromatous abscesses or calcified plaques were seen with the unaided eye. Contrary to atherosclerosis as found in blood vessels, proliferation of vascular connective tissue was never noticed in the diseased heart valve. Blood vessels were entirely lacking around the deposits of cholesterolin crystals and calcium, and no scar tissue was formed. The complete absence of reactive processes and of destructive lesions in atheromatosis of the heart valves is in striking contrast to lesions as observed in arteries.

COMMENT

There are five papers⁶⁻¹⁰ in the literature dealing with atheromatosis of the mitral valve. While all observers agree in the exclusive involvement of the ventricular side of the large mitral leaflet, the significance of this fact has apparently been overlooked. Its importance in regard to the genesis of atherosclerosis cannot be overestimated. This observation disproves at least six theories which play an important role in recent discussions of the atherosclerosis problem.

1. The predilection of the process to the ventricular side of the leaflet does not support the theory that arteriosclerosis is a manifestation of a specific disease of fibroelastic tissue throughout the body, caused by wear and tear (Kolen¹¹). Both sides of the mitral leaflet have identical arrangement of collagenous and elastic fibers and are subject to the same degree of wear and tear.

2. The localization of the lipid deposits is in contradistinction to Hueck's¹² theory that changes in the hydrogen-ion concentration of the ageing intima lead to the process of atherosclerosis. There can be no difference in pH between the ventricular and auricular layers, since both have the same histologic structure and are suspended in the same nourishing medium, namely, arterial blood.

3. The site of the yellow spots disproves the assumption of Winternitz, Thomas, and LeCompte, who believed that rupture of vasa vasorum initiates the process of atherosclerosis. There are no blood vessels in the free portion of the normal mitral leaflet; occasionally in the upper third, blood vessels may be encountered accompanying muscle bundles, and, in cases of rheumatism, they may be found in the other parts of the cusp. However, such vessels as are in the leaflet are seen only on the auricular side, i.e., just opposite the localization of yellow spots.

4. The complete absence of proliferation of fibrous tissue, which is characteristic of atheromatosis of the mitral valve, does not substantiate the assumption of Jores,¹³ who believed that fibrous thickening of the intima invites the precipitation of lipid. In mitral valves, a new formation of connective tissue does not exist, but deposits of cholesterolin, formation of cholesterolin crystals, and calcification occur as in blood vessels.

5. My findings do not support the view held by Duff¹⁴ that a primary degeneration of the ground substance of the intima is the essential cause of arteriosclerosis and that it precedes the precipitation of lipoids. An alteration of the ground substance on the ventricular side only, with subsequent lipoidosis, seems very unlikely.

6. The predilection of the yellow spots to the ventricular layers is not in accord with the view held by Jones and Rogers¹⁵ that the endothelium may become permeable for cholesterol after injuries by bacterial influences. Bacterial lesions are, as a rule, found on the auricular side of the mitral valve.

The results of my own studies are in accord with the conception of Anitschkow that precipitation of lipoid in the ground substance is the essential cause of atherosclerosis and that it occurs without previous degeneration of the ground substance.

The whole problem of atherosclerosis then hinges upon the question of why lipoids precipitate from the nutrient fluid in the ground substance. Since the lipoids enter the tissue of the leaflet on the ventricular and auricular side with the nourishing blood plasma, the question is "Why do they precipitate only on the ventricular side?"

The lipoids appear in the nourishing fluid in colloid solution. There have to be certain factors which disturb the stability of this colloid solution on the ventricular side. With every ventricular systole, the colloid solution in the tissue of the mitral leaflet is subjected to vigorous percussions. The fluid waves which start from the ventricular surface of the leaflet are broken at the fibrous middle plate, and the fluid in the ventricular fibroelastic layer suffers repercussions in opposite direction. From the fundamentals of colloid chemistry it seems plausible that these mechanical forces are responsible for the precipitation of lipoids in the ground substance of the ventricular layers. The importance of mechanical influences on the precipitation of colloid particles is known from flocculation tests. Kahn,¹⁶ who studied in detail the shaking principle in flocculation tests, demonstrated that excessive shaking leads to flocculation of lipoids even in normal sera.

SUMMARY

The morphologic findings in 100 mitral valves with atheromatosis are presented. Anitschkow's view, that precipitation of lipoids in the ground substance is the primary event of atherosclerosis and is not preceded by degeneration of the tissue, is accepted.

Lipoids enter the leaflet with the nourishing blood plasma, in colloid solution. The localization of the atheromatous lesions on the ventricular side of the leaflet refutes many theories on the cause of arteriosclerosis and suggests the importance of mechanical factors. The nourishing fluid in the ventricular layers of the mitral leaflet is subjected to percussions and repercussions during each systole, and precipi-

tation of lipoids occurs by mechanical disturbance of the colloidal state of the lipoids in the ground substance.

While precipitation of lipoids, formation of cholesterol crystals, and deposits of calcium occur in atheromatous heart valves just the same as in blood vessels, proliferative changes are absent due to the lack of blood vessels in the ventricular side of the mitral leaflet.

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DYNAMICS OF BLOOD FLOW IN THROMBOANGIITIS OBLITERANS

MILTON LANDOWNE,* M.D.
CHICAGO, ILL.

IN THROMBOANGIITIS obliterans, although changes occur in the veins and about nerves, the essential lesion is an irregular reduction in the luminal diameter of the arteries,¹ and therapy has been largely directed toward relieving the ischemia which results. Vasodilatation is the purpose of many of the methods used in treatment. It is held²⁻⁴ that by vasodilatation the development of a collateral circulation will be augmented, and the nutrition of the limb improved. In addition, it has been thought²⁻⁷ that an increase in the amount of blood flowing to the limb may be brought about by these vasodilating mechanisms. It might be possible, therefore, by measuring the volume flow of blood to such limbs, to learn what methods relieve spasm, encourage regressions of the lesion, or generally increase the blood flow to the region. Obviously, certain important information would not be obtained by measuring blood flow. No evidence would be elicited concerning the state of nutrition of any local part or the distribution of the blood flow within the limb. An area of skin which is potentially gangrenous may receive an increased supply of blood, and heal completely at the expense of the circulation elsewhere within the limb (muscles, A-V shunts, etc.), and at no time need the *total* supply of blood to the limb have been increased. Dilatation of vessels in response to a stimulus might not be detected unless this were associated with an increase in flow. Simultaneous vasoconstriction in one area and vasodilatation in another would provide this situation, and it is one of the purposes of this communication to emphasize that even dilatation alone may not be reflected by increased flow under certain conditions imposed by disease. Therefore, clinical improvement cannot a priori be judged simply from measurements of the blood flow to the resting limb, and, because of the unknown and variable factor of distribution of blood within the limb, might not even be reflected by measurements of the blood flow to the limb after maximal vascular dilatation had been induced.

It is further to be noted that a change in blood flow per minute which may be insignificant by comparison with the sensitivity of the method, or with the magnitude of variations in flow, nevertheless, over a period

From the Cardiovascular Department, Michael Reese Hospital, Chicago.
Aided by the A. D. Nast Fund for Cardiac Research and the A. B. Kuppenheimer Fund.

Received for publication Dec. 27, 1941.

*Emanuel Libman Fellow.

of days or months, can provide a total increase in blood supply which may be significant with respect to survival of tissue. To illustrate, an average increase in blood flow of 0.1 c.c. per min. per 100 c.c. of limb would result in one day in an increase of 144 c.c. in the amount of oxygen delivered to each 100 c.c. of limb. Finally, although a change in the effective peripheral resistance is reflected in a change in blood flow, the reverse is true only when cardiac output and blood pressure are constant.

Kunkel and Stead⁸ have demonstrated that in thromboangiitis obliterans the "maximal" blood flow (that which results from keeping the temperature of the limb at 43° C. for thirty minutes or more) is reduced, and have presented a general correlation of the values for maximal flow with the presence and severity of symptoms. Abramson, et al.,⁹ obtained values in agreement with these. They have recently reported¹⁰ that certain procedures will not increase blood flow. Our own observations are in complete accord with theirs. We have studied the blood flow in the legs of subjects with thromboangiitis obliterans and have investigated the response to temporary arterial occlusion.

METHOD

Blood flow was measured in the leg-foot of resting subjects in the horizontal position by an improved modification¹¹ of the plethysmographic method of Hewlett and Van Zwaluwenburg.¹² This depends upon the theoretical principal that, if venous return be prevented abruptly (by inflating a cuff about the calf to a level below diastolic, but above venous, pressure), the limb will increase in volume. The initial rate of increase in volume should represent the rate of arterial inflow which was present just before the measurement was made. The foot and lower part of the leg were encased in an air-containing, insulated plethysmograph. A thin, nonconstricting rubber diaphragm was cemented to the leg and stretched over the opening, and this closure was made rigid by a plaster of paris backing. Volume changes were transmitted via a short vertical tube to a counterbalanced celluloid spirometer, damped in a glycerine-water mixture. A long lever wrote in ink on kymograph paper. In this manner, changes in the volume of the portion of limb within the plethysmograph were recorded upon the kymograph. Temperature was recorded. Calibration was carried out by means of a syringe which was connected directly to a side tube. Although the form of the pulse wave was not accurately reproduced, pulsations were visible in the records on normal subjects. These were almost always absent in records from patients with thromboangiitis obliterans or arteriosclerosis obliterans.

A narrow (5 cm.) pneumatic cuff was placed about the leg, just proximal to the plaster seal. When this was abruptly inflated, the spirometer recorded an increase in volume. The initial slope of this rising curve was ascertained by drawing a "tangent" line, and was expressed as θ , = the horizontal distance in millimeters traversed by the kymograph paper for a 4 c.c. increase in volume as measured on curvilinear ordinates. This was converted to blood flow in terms of cubic centimeters per minute per 100 c.c. of limb volume by the following expression:

Blood flow = $\frac{400 S R}{V \theta}$ c.c./min./100 c.c. limb volume, where V = limb volume;

S = paper speed in mm./min.; R = calibration factor; θ = tangent in mm./4 c.c.

For a given experiment, at each speed used, $\frac{400 S R}{V}$ is a constant. Each measure-

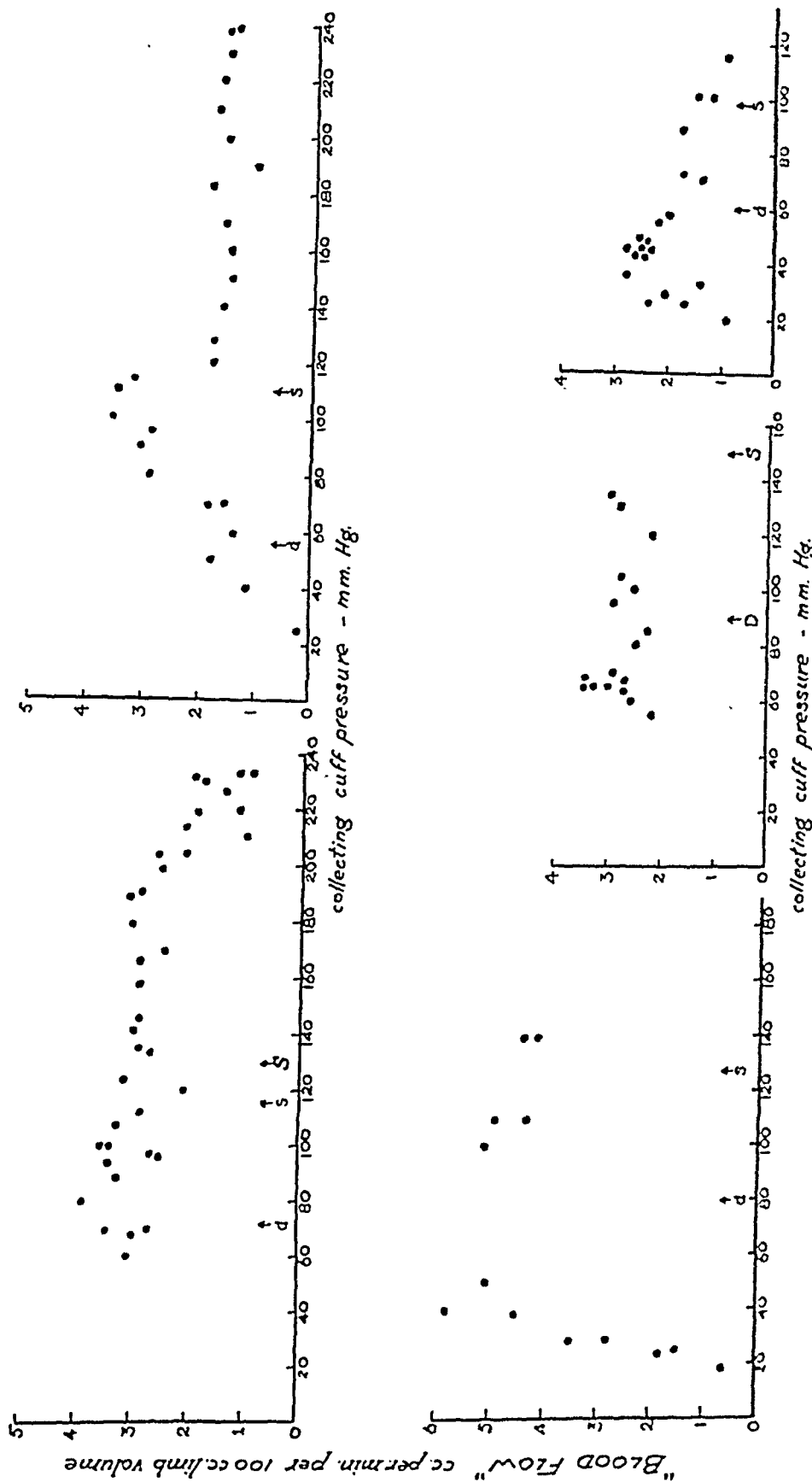


Fig. 1.—The effect of varying "collecting cuff" pressure upon the recorded blood flow in the foot-leg of subjects with thromboangiitis obliterans. The systolic and diastolic blood pressures in the popliteal artery are indicated by S and D, or in the brachial artery by s and d, respectively, in each case. Discussed in text.

ment of flow may be completed within about three to seven seconds, and repeated as often as every ten or fifteen seconds.

The validity of this method depends upon (a) the completeness of the venous occlusion, (b) the absence of initial obstruction to arterial inflow, (c) the distensibility of the vascular system and of the limb, and (d), in any system, the ability of the recording system to register rates of change in volume accurately. Many workers, as well as ourselves, have studied the limitations of the method.^{8, 9, 11} These studies have indicated that consistent results may be obtained in normal persons. No insistence is made by us as to the degree of absolute accuracy of these values. Conformity, sensitivity, and predictable behavior appear to indicate that the apparatus is suitable for measuring blood flow to distal parts of normal extremities.

It was necessary, however, to ascertain whether the method is applicable to diseased limbs. With reference to the first three points above: (a) In thromboangiitis obliterans, veins with thickened walls might be less easily occluded by the cuff pressures used, and collateral venous flow may not be as easily accessible to occlusion by the cuff pressure. (b) Small collateral arteries, with thinner walls and under lower pressures, may be occluded, at least in part, by the application of a collecting cuff. (c) The walls of thickened veins are less distensible and venous space is diminished. Tissues are more rigid and less distensible. Venous stagnation is not uncommon.

The following observations were made upon the extent to which these factors interfered with the use of the method. The increase in volume which occurred upon application of the collecting cuff to subjects with thromboangiitis obliterans was as prompt as in normal subjects. It continued, without appreciable decrease in slope, as long or longer. The resting rate of blood flow was of the same order of magnitude as in the normal subject. As the pressure used in the collecting cuff was varied, the recorded blood flow was greatest over a certain range (Fig. 1), just as in the normal. The optimal pressures which were required varied from patient to patient, and ranged from 30 mm. upward. As the cuff pressure was increased above the diastolic level, the recorded blood flow did not always decrease. Pressures above the estimated systolic pressure in the popliteal artery still resulted, in some subjects, in sizable recorded flows. This also was noted in normal subjects, but it apparently required higher pressures in the narrow cuff about the calf to reduce or abolish arterial inflow (Fig. 1). This was true also when a wide cuff was applied about the thigh for the purpose of occluding inflow; a slow volume increase of the foot-leg was noted after inflation of such a cuff to well above brachial systolic pressure (200 to 300 mm. Hg). Inflation of the lower cuff to 50 to 70 mm. Hg would then reveal the magnitude of this slight inflow of blood.

These observations would indicate (1) that venous obstruction produced by inflation of the collecting cuff was as adequate in patients with thromboangiitis obliterans as in the normal subject, (2) that arterial inflow was not significantly obstructed during measurements, and (3) that it was more difficult to completely occlude arterial inflow by pressure cuffs.

The distensibility of vessels also appears adequate for the application of the method, for the volume curve rises steadily. It remains possible that, if the limb was previously congested, such congestion would interfere sooner with initial inflow of blood when the cuff was applied to obstruct venous return. This would cause the recorded flow to be erroneously small. The actual flow might be low in such a congested limb, but the degree of reduction would be exaggerated by any such inadequacy of the method. To test this, congestion of the leg was produced deliberately, and to a degree greater than that which occurred during the course of any experiment. Blood flow was measured repeatedly after release of congestion, and was never less than control values for more than thirty seconds; the average

duration of any decrease was less than fifteen seconds (Fig. 2A). Hence it is concluded that, as in normal limbs, congestion may result in reduced flow and/or introduce an error, but, if any such artifact is present, it does not persist longer than thirty seconds after release of the congesting force. The relevant data are presented with the experiments to which they are pertinent.

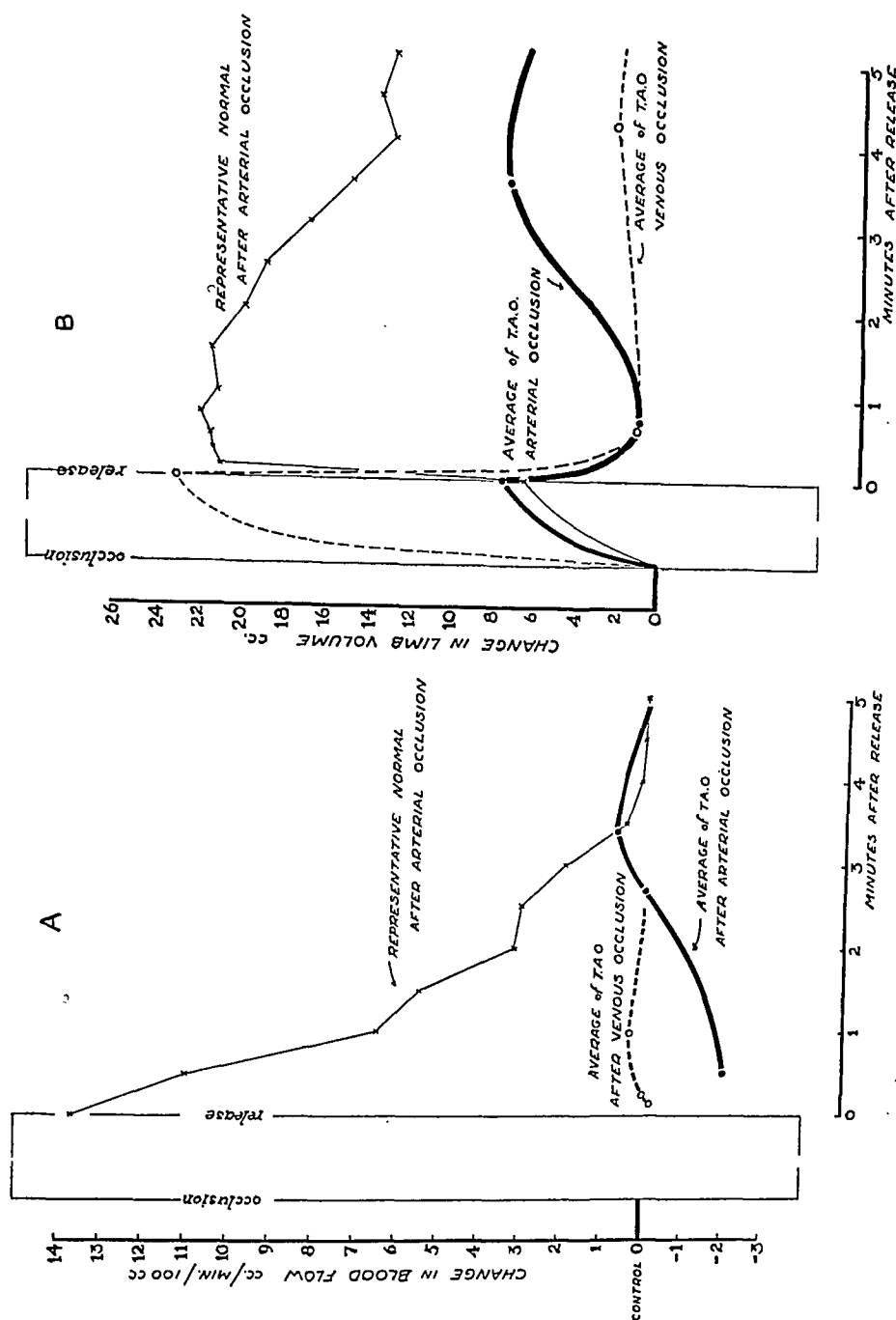


Fig. 2.—The change in blood flow after the release of arterial occlusion (A), and the change in volume of the limb during and after the same procedure (B). The heavy line indicates the average of changes after release of eighty-nine arterial occlusions (average duration of occlusion, 7.9 minutes) (see Table I), and the broken line indicates the average of changes after release of deliberate congestion produced by twelve venous occlusions (average duration, four minutes) in subjects with thromboangitis obliterans (T.A.O.). The light line indicates a representative experiment on a normal subject (arterial occlusion of six minutes).¹¹ Actual flows or volumes are not shown on this chart; only the change in flows and volumes are shown. Discussed in text.

Experiments were carried out (as on normal subjects¹¹) in the following manner. The patient rested in bed, with the leg (usually the left) within 10 cm. of heart level. After thirty minutes a series of resting flow measurements were made, usually at intervals of thirty seconds, and over a period of five to fifteen minutes. The effect of arterial occlusion upon volume and flow was observed by abruptly inflating (from a pressure tank) a 16 cm. cuff about the thigh to 200 to 350 mm.

Hg, and maintaining this occluding pressure for varying periods of time. Any incompleteness of occlusion was revealed by an increasing limb volume during the period of occlusion. Upon release of the occluding cuff, repeated measurements of flow were made at intervals of fifteen to thirty seconds, and then less frequently for two to fifteen minutes. Occlusion and release were repeated, usually for the same or different periods, one or more times. In this manner the effect of varying occlusion pressure or occlusion time could be related to the initial flow caused by release, the maximal flow observed, the changes in flow and their duration, the changes in limb volume, and visual and subjective notations. In several experiments, heart rates were recorded.

The effect of heat, either alone or in combination with occlusion, was also studied. Heating to 40 to 45° C. for thirty minutes preceding and between measurements was accomplished by a thermostatically controlled hot-air blower, which was detached during measurements. In these experiments no observations on basal volume change were made. The volume changes caused by temperature variation during the three to seven seconds which were necessary for each measurement were not significant, as was demonstrated by observing the volume change over an equal period preceding and following the measurement.

Observations during forty-six experimental periods, comprising measurements of blood flow before, during, and after eighty-nine trials of arterial and twelve of venous occlusion of the leg in seven cases of thromboangiitis obliterans are summarized in Table I. The subjects were men between the ages of 32 and 54 years. All were ambulatory, coming from home, or hospitalized for ganglionectomy, and had mild to moderate symptoms. No active phlebitis was manifest. Two patients presented trophic lesions, which healed with hospitalization and ganglionectomy, and one had a recently healed lesion.

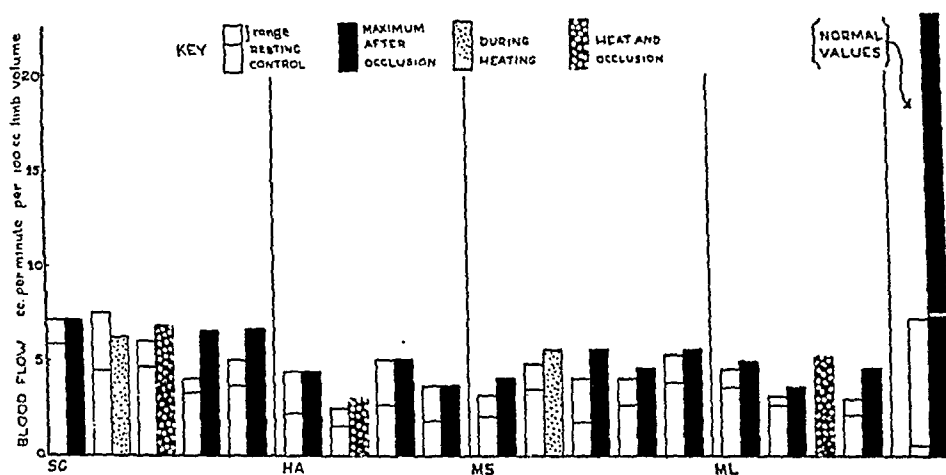


Fig. 3.—Illustrative examples of blood flow in the foot-leg of subjects with thromboangiitis obliterans at rest, and after dilating procedures, as compared with average of values for normal subjects.¹¹ Discussed in text.

The resting flows ranged from 1.1 to 7.5 c.c./min./100 c.c. of limb volume (Fig. 3). The minimum range in each experimental period was 0.4 c.c., the maximum, 3.2 c.c. In an attempt to increase the blood flow by inducing reactive hyperemia, a cuff about the thigh was inflated to a pressure of 200 to 300 mm. Hg, and this pressure was maintained for one-half to fifteen minutes; the maximum resulting flows ranged from

B. Venous Occlusions

No. of trials of occlusion	12	0	4	3	3	0	0	0	2
Duration of occlusions (range in min.)	1-11	---	1-5	5-11	1-5	---	---	---	2
Av. duration of occlusions (min.)	4	---	4 1/4	7 3/4	2 3/4	---	---	---	2
Av. magnitude of decrease in flow (c.c./min./100 c.c.)	0.2	---	0.3	0.3	0.9	---	---	---	0.4
Av. duration of any decrease (min.)	< 1/4	---	1/30-1/2	1/4-1/2	1/30-1/4	---	---	---	0-1/2
Av. maximal increase in flow (c.c./min./100 c.c.)	0.3	---	0	0.5	0.4	---	---	---	0.4
Av. time after release at which maximal increase was manifest (min.)	1	---	---	3 3/4	---	---	---	---	2 3/4

CHANGE IN LIMB VOLUME

A. Arterial Occlusions

No. of trials in which volume change was determined	68	3	15	14	18	7	7	7	4
Av. increase in volume during occlusion (c.c.)	7.6	7	10	5	13	2.5	1.5	1.5	10
No. of trials in which decreases in volume occurred after release of occlusion	51	3	15	8	15	6	0	0	4
Av. extent of decreases in volume (c.c.)	6.7	7	15	2	5.6	7	0	0	9.4
Av. duration of decreases in volume (min.)	2 3/4	1/2	1 1/4	1/2	5/8	1 1/2	---	---	1 1/2
No. of trials in which increases in volume occurred	61	3	13	13	14	7	7	7	4
Av. maximum extent of this increase (primary or secondary) (c.c.)	6.5	11	9	5	4.3	6.5	7	7	8
Av. time at which maximum increase occurred (min.)	3 1/2	3	6 1/2	3 3/4	2	4 1/2	1 3/4	1 3/4	1 3/4

B. Venous Occlusions

No. of trials in which volume change was determined	12	0	4	3	3	0	0	0	2
Av. increase in volume during occlusion (c.c.)	23	---	30	24	12	---	---	---	25
No. of trials in which decreases in volume occurred after release of occlusion	12	---	4	3	3	---	---	---	2
Av. extent of decreases in volume (c.c.)	22	---	27	22	14	---	---	---	25
Av. duration of decreases in volume (min.)	5/8	---	3/4	1 1/4	1/2	---	---	---	7/8
No. of trials in which increases in volume occurred	4	---	0	3	1	---	---	---	0
Av. maximum extent of this increase	1 1/4	---	0	4	3 1/2	---	---	---	0
Av. time at which maximum increase occurred (min.)	4.2	---	---	4	5	---	---	---	---

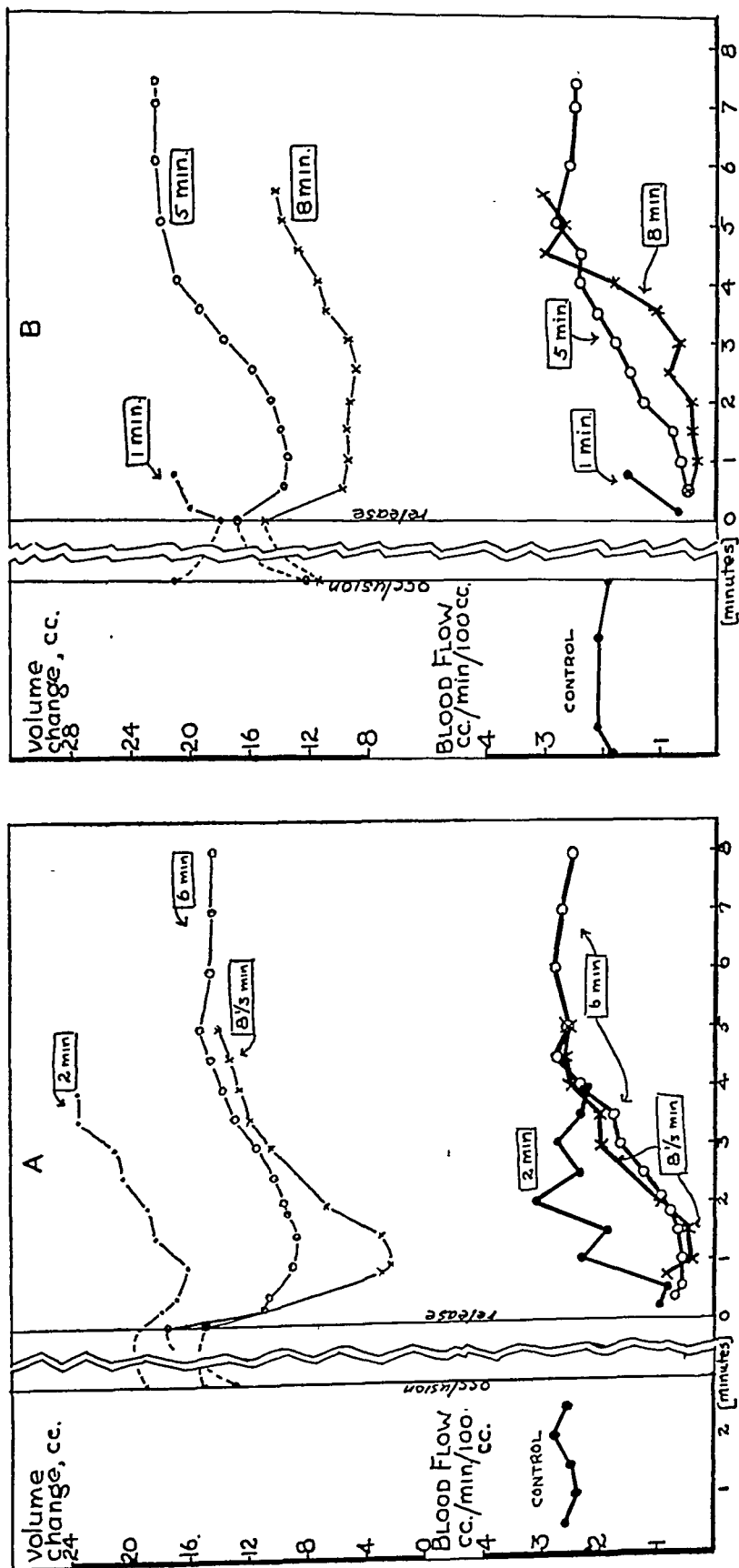


Fig. 4.—The effect of lumbar sympathectomy upon the resting and "maximal" blood flow in the foot-leg of a subject with thromboangiitis obliterans. The resting control flow, the flow after release of arterial occlusions of comparable durations, and the changes in limb volume after the release of these occlusions are shown in A prior to, and, in B, one week after, lumbar sympathectomy. The duration of the occlusion which preceded each curve is indicated on the several curves. Discussed in text.

2.5 to 7.6 c.c. (Fig. 3). The greatest increase in flow in any case was but 3 c.c. The maximal increase after release was less than 1 c.c. following fifty-nine trials in thirty-six experimental periods, and was equal to, or greater than, 1 c.c. in thirty trials.

In a series of observations on thirteen normals,¹¹ the resting flows were similar, i.e., 0.5 to 6.0 c.c./min./100 c.c., but the maximal flows after release of arterial occlusion were 7.3 to 22.6 c.c./min./100 c.c. (Fig. 3).

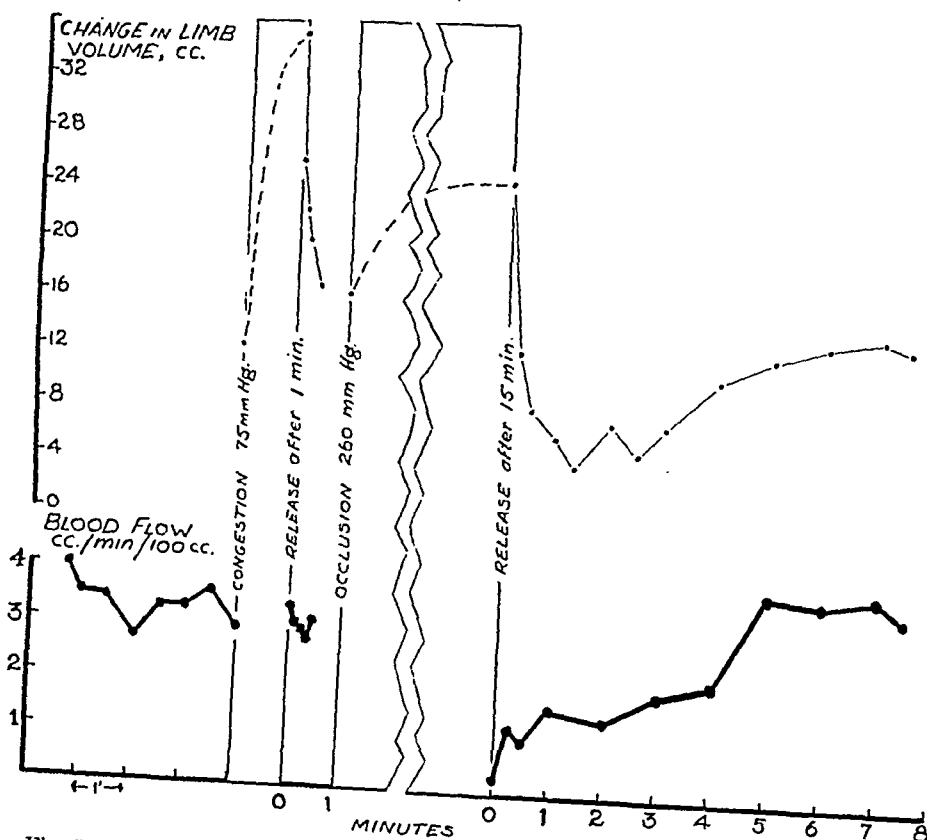


Fig. 5.—Comparison of the effect of congestion (by venous occlusion for one minute) and ischemia (by arterial occlusion for fifteen minutes) upon the blood flow and limb volume of the foot-leg in a subject with thromboangiitis obliterans. Discussed in text.

Heating the limb to evoke maximal dilatation, in ten experiments upon six patients, or combined heating and arterial occlusion, in ten trials in eight experiments on five patients, did not significantly alter the resting level of blood flow.

Lumbar sympathetic gangliectomy, which was performed on three patients, did not alter significantly either the resting blood flow of the ipsilateral foot-leg nor the response to arterial occlusion, although a distinct increase in skin temperature was noted (observations made about one week after operation) (Fig. 4).

Unexpectedly, we observed (Figs. 2, 4, Table I) that, instead of the immediate increase in flow noted normally (Fig. 2), the release of

arterial occlusion in some cases was followed by a decreased blood flow; the maximum decrease was equal to, or greater than, 1 c.c. in forty-six trials in twenty-nine experimental periods. In thirty of these forty-six trials, a decreased blood flow was present for two minutes or more. The average of the maximal decreases in all cases was 1.8 c.c. The average time after release of the occlusion during which a decrease was manifest was 2.7 minutes.

During occlusion a volume increase sometimes occurred. Deliberate congestion of the limb at the beginning or at the end of the period of occlusion, or without occlusion, which produced a large volume increase (Fig. 5), demonstrated that the factor of congestion did not vary the results for more than thirty seconds after the occlusion had been released. The average maximal decrease in flow caused by deliberate congestion in twelve instances of venous occlusion was 0.2 c.c., and lasted less than fifteen seconds after release of the occlusion (Fig. 2). For purposes of clarification, and to avoid this questionable factor, the calculations of the decrease in flow after release of arterial occlusion without deliberate congestion were based only on measurements which were made thirty seconds or more after release.

The initial decrease in flow after release of arterial occlusion was investigated further in a few experiments. In ten instances, heating the plethysmograph to 40 to 43° C. for at least thirty minutes before, and maintaining this temperature during arterial occlusion did not modify the results significantly. After release of occlusions which averaged 9.4 minutes, the maximal decrease in flow averaged 2.2 c.c., and the decrease persisted for an average time of 2.4 minutes. The response before and after lumbar sympathetic ganglionectomy was also compared in three cases. The average maximal decrease in flow after release of the arterial occlusion (average duration, 7.2 minutes) was 1.2 c.c., and the average duration of any decrease was 1.6 minutes, in ten preoperative trials. One week after the ipsilateral removal of the second, third, and fourth lumbar sympathetic ganglia, the average of seven trials on these patients indicated an average maximal decrease of 1.8 c.c., and an average duration of any decrease of 2.4 minutes (Fig. 4).

The changes in limb volume after release of arterial occlusion were calculated in sixty-eight instances (Table I). Primary decreases in volume occurred fifty-one times; the maximum of each ranged from 0.5 to 22.5 c.c., averaging 6.7 c.c., at an average time of $\frac{2}{3}$ minute after release. In the control group there was an immediate increase in volume, which was sustained (Fig. 2). In the subjects with thromboangiitis obliterans, an increase, delayed in onset, occurred in sixty-one trials. The maximal increase averaged 6.5 c.c. above the lowest volume level—a return just about to the volume at the time of release of the occlusion. The average time after release that the volume regained this level was 4.2 minutes.

In twenty-one trials the heart rate was noted, either by timing ten pulse beats with a stop watch (nine trials), measuring the rate recorded in fifteen seconds on an electrocardiograph (nine trials), or calculating

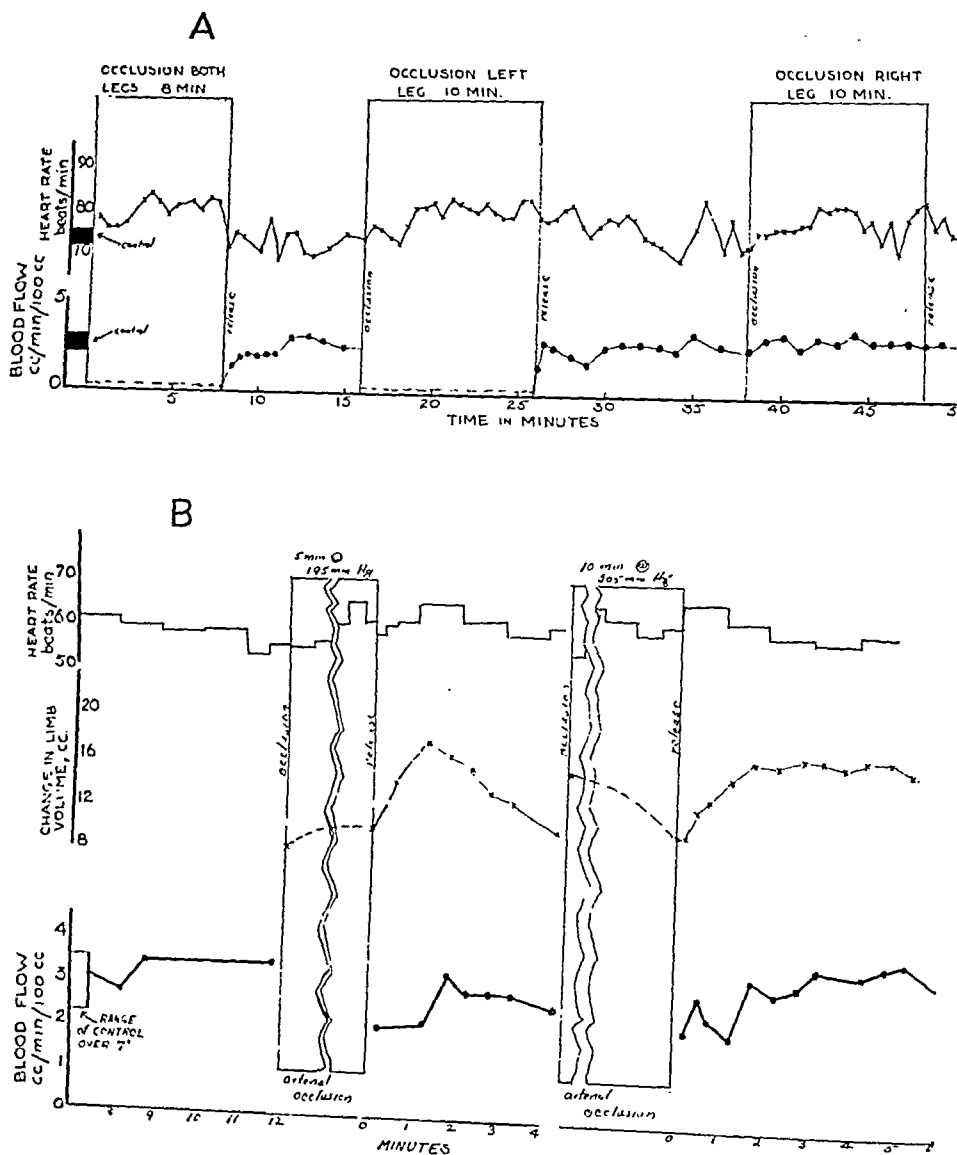


Fig. 6.—A. The effect of arterial occlusion of the same and of the contralateral leg upon the blood flow in the left foot-leg, and upon the heart rate, of a subject with thromboangiitis obliterans. B. Heart rate, limb volume change, and blood flow, as affected by occlusion and release of arterial circulation to the leg of a subject with thromboangiitis obliterans. Discussed in text.

the rate from the cycle length of each beat (three trials). The occlusions were seven to fifteen minutes in duration (averaging eleven minutes). The change in heart rate upon release of occlusion (Fig. 6) was from -10 to +10 beats/min., averaging +1 beat. In a series of normal subjects¹³ the change in rate was +7 to +35, averaging +20 beats/min.

DISCUSSION

The number of patients whom we studied is too small to warrant an attempt to establish a correlation of resting or maximal flows with the clinical manifestations. The results are comparable to those of Kunkel and Stead,⁸ for our results fit into the range of maximal blood flow indicated by these authors to correspond with the severity of the disease. In general, the slight increases in flow which occurred in response to vasodilating procedures were in the milder cases. The larger initial decrease in flow after release of arterial occlusion occurred in the more severe cases. Observations over control and therapeutic periods totaling three to ten months did not reveal striking alterations in resting and/or maximal flows in the cases studied, or with therapy used, although various degrees of clinical improvement, objective as well as subjective, were noted.

The resting values obtained by us are of the same order of magnitude as the "maximal" values. In other words, arterial occlusion or heat, when used as a dilating agent, did not effect any significant augmentation in recorded blood flow in the patients with thromboangitis obliterans whom we studied. These agents induce "maximal" dilating mechanisms in the normal subject.

The absence of any comparable cardiac acceleration or limb volume increase after release of arterial occlusion corroborates the observations that the blood flow is not increased.¹³

These results indicate that the procedures which were used did not significantly reduce the effective peripheral resistance in these subjects. To explain this we can postulate that, *in spite of widespread dilatation of smaller vessels, the fixed narrowing of the larger vessels (arteries) offers proportionately so much resistance that the more peripheral dilatation does not effectively reduce the total resistance to flow.*

In order to understand how this last mechanism operates it is important that several considerations be presented. In any vascular segment, some resistance to the movement of blood is encountered at every point along the vascular tree. The distribution of this resistance is not uniform. Normally it is predominantly located in the arterioles, just before the smallest vessels. Because of this distribution, the mean blood pressure in the limb vessels falls but little until the small vessels are encountered. Here, over the relatively short distance from smallest arteries to capillaries, a fall in pressure of 50 to 80 mm. Hg occurs.¹⁴

When the lumen of any vessel is narrowed, resistance to flow is increased. The factors which govern the precise relationship of frictional loss to the vessel diameter are complex.¹⁵ As a crude approximation for either laminar or turbulent flow, this resistance varies inversely with at least the third power of the radius. Distortions and lengthening of the vascular pathway also increase resistance. When the lumen of a vessel is sufficiently narrowed, as by arteritis, atheroma, etc., the

increased resistance of the large vessels may become a predominant proportion of the total vascular resistance. In such a case the gradient of pressure would fall steeply in these narrowed regions. If all the resistance of the distal peripheral vessels could be removed, as would

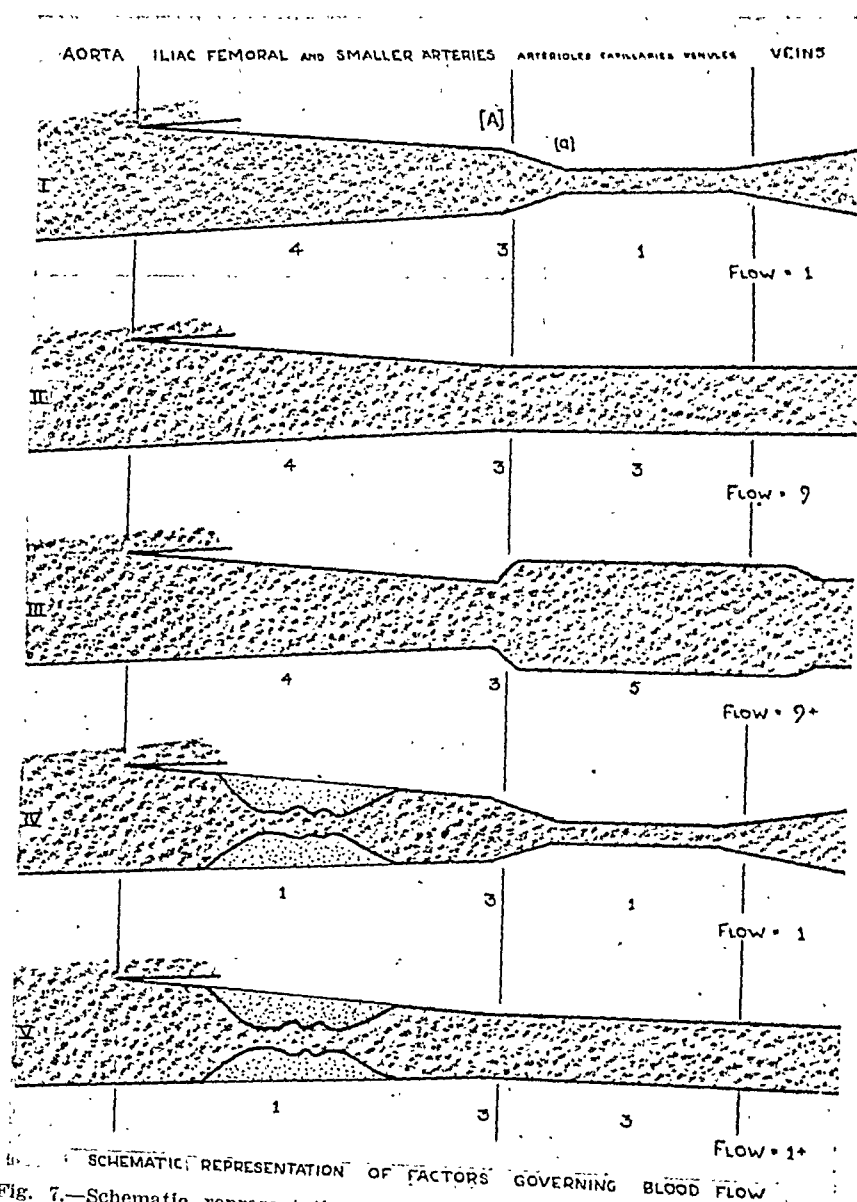


Fig. 7.—Schematic representation of some factors governing blood flow. I, II, and III represent degrees of peripheral vascular dilatation in the normal, and IV and V represent states similar to I and II in thromboangitis obliterans. The proportional radii of each vascular segment are indicated by the numbers under each diagram. The relative flow is suggested by the figure to the right of each diagram. Discussed in text.

occur upon amputating the leg, the initial escape of blood would not be as large as in a normal limb. The amount of this initial flow would depend (just as in the normal) upon the caliber of the opened vessels and the pressure within them. The initial escape would represent the maximal blood flow which could have been supplied to the tissues of

that leg. Although constriction of peripheral vessels would have reduced this flow, dilatation could not have increased it beyond this maximal value (Fig. 7 IV and V).

It follows, therefore, that, when progressive dilatation of small vessels occurs, a point may be attained beyond which further dilatation is not attended by an appreciable increase in blood flow. This would mean that the size of some proximal vessel is now the factor which limits the magnitude of flow. This, for instance, may be of importance when reactive hyperemia after release of arterial occlusion fails to increase further the volume of blood flow in a normal limb whose skin vessels have been previously dilated by heat¹¹ (Fig. 7 I, II, and III).

In thromboangiitis obliterans, the narrowing of the arterial lumen (whether entirely or only partially organic) thus eventually determines the maximum amount of blood which can be delivered to the tissues at a given arterial pressure. Beyond this, the state of the peripheral vessels may regulate this flow, reduce it, or distribute it, but cannot increase it. As blood flow is further restricted, a point is reached at which ischemia sets in, at first only when the demand for blood exceeds normal, e.g., during exercise; but, as the disease progresses, the limb at rest may come to require all the blood that the major supplying vessels can transmit. At this point, the peripheral vessels may be in a normal state of activity, or, and this is more likely, they may be dilated.^{1, 16} In either event, the impediment to flow is located largely in the major vessels, instead of in the small ones. Finally, with advanced disease, even the minimal normal flow in the resting extremity cannot be forced past the arterial obstruction, and nutrition becomes insufficient to meet the needs of the tissues.

In short, the concept which fits the observations made by us may be summarized as follows: The resting blood flow in limbs affected with thromboangiitis obliterans may be normal, except in severe cases. Dilatation of peripheral vessels will result in an increase in flow only up to the limits imposed by the narrowed arterial lumina. Although in early cases this may permit a significant increase, in manifest cases (in which symptoms of insufficient circulation are evoked by a demand for increased blood), no significant augmentation of blood flow will follow peripheral dilatation.

However, it may be argued that these dilating procedures failed to produce peripheral vasodilatation in our patients, or that any dilatation produced in part of the limb vessel is neutralized by a concomitant and equal vasoconstriction in other parts. This would occur if spasm* were present and unrelieved by the dilating procedure, or if the vessels themselves responded in an abnormal manner.

*Spasm is considered here to represent an undue or disadvantageous degree of vasoconstriction, leading to a reduced blood flow. Vasoconstriction may be present in the diseased limb,¹⁵ and serves to divert the limited blood supply to those regions with the greater demand for blood. General dilatation of peripheral vessels may lessen this advantageous redistribution, and, if more blood is diverted to the skin, the skin temperature may rise even when the total flow to the limb is unchanged. This is not to be considered as spasm, and, therefore, caution must be applied in interpreting skin temperature observations.

It has generally been assumed that the procedures which we used (heat, ischemia, and sympathectomy) abolish vasoconstrictor stimuli, either local or of reflex origin.¹⁷ Increased irritability of the contractile elements of blood vessels in the presence of a defective circulation has been suggested²⁰⁻²² from studies of depletion of circulation in animals, of the production of Bier's spots in man, and on vasospastic disorders.²²

It is conceivable, for example, that a given degree of reduction in oxygen tension may give rise to contraction of an abnormal muscle preparation, although, under normal circumstances, it produces relaxation. The same stimulus may evoke a different response when the condition of the tissue or its environment is altered. Morphologically, little or no alteration has been described in the smallest vessels^{1, 19, 23, 24} in thromboangiitis obliterans. This does not mean that physiologic abnormalities may not exist. However, as shown in skin areas by temperature, color, and microscopic observations, local dilator and constrictor agents appear to elicit responses in the normal direction.¹⁸

Buerger has stated,¹ (page 74) "Vaso-constriction and even vasodilatation are usual and common sequences of obstructive anemia or ischemia.

(Page 240) "Too much emphasis cannot be laid on the fact, however, that most of the objective symptoms regarded by many authors as of neurotic foundation, are merely hydrostatic and compensatory phenomena, although . . . independent vasomotor disturbances may be concomitant . . .

(Page 247) "The conclusion is warranted that the finer vessels are still able to respond, and are not wholly inert and paralytic."

We consider, therefore, that the primary factor limiting the maximal blood flow in our cases of thromboangiitis obliterans was not failure to dilate the small vessels, but the narrowed caliber of the major vessels—the involved arteries—so that, even with peripheral vascular dilatation, the supply of blood to the part was restricted. In any given case this is amenable to investigation by measuring flow before and after dilatation of peripheral vessels is actually produced by a suitable method.

The fact that there is an initial decrease in flow after release of arterial occlusion lends support to the consideration that there may not be an unqualified dilatation in response to ischemia in the limb vessels. Whatever the origin of this decrease, our evidence indicates that it is not abolished by heat or sympathectomy. Therefore, it is to be postulated that this decrease may be evoked by a constrictive response of the peripheral vessels, or of peripheral axons, resulting from deprivation of the mechanical or chemical stimulus of circulating blood; or it may follow direct major vessel or local neuraxon stimulation produced by the occluding pressure of the thigh cuff on the underlying arteries or nerves. The fact that peripheral heat does not reverse this response suggests perhaps that the central rather than the peripheral vessels are con-

cerned. The response seems to be evoked more definitely by longer periods of occlusion (Fig. 8) and is dissipated by re-establishment of circulation. The response may not be peculiar to this disease. It may, in fact, occur in normal subjects. For example, if it is in response to the pressure applied to the major artery, resulting in a narrowing due to local spasm, this may be of a degree which, in a normal vessel, will not significantly increase the total resistance of the hyperemic limb. The same amount of circumferential shortening of muscle fibers may effect an appreciable increase in total resistance in an already narrowed vessel. We have, however, no evidence that this is the case in the normal subject. The mechanism of the initial decrease in flow may be related to that underlying the production of Bier's "white spots" and "ischemic patching."²⁵ Rous and Gilding,²¹ Krogh,²⁶ Wolf,²⁷ and Lewis²⁸ have contributed evidence that these areas of paling occur with prolonged ischemia. Several of the earlier authors have suggested the unsupported hypothesis that asphyxial blood may cause constriction before dilatation.²⁹

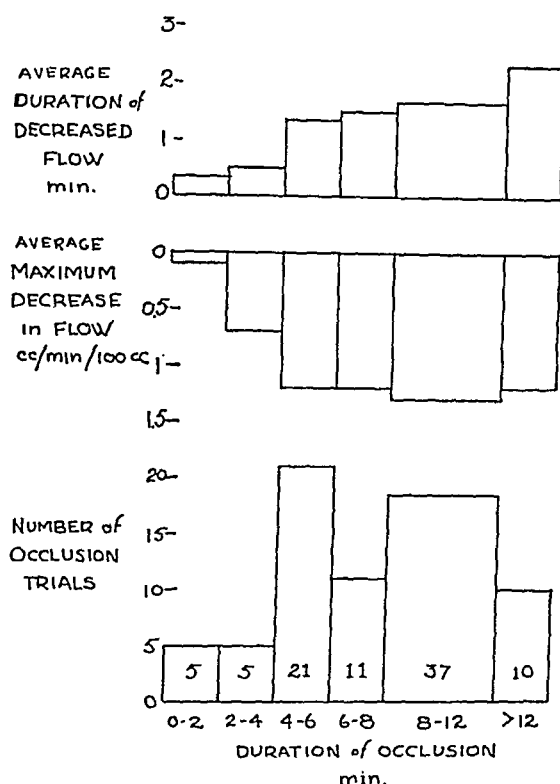


Fig. 8.—Chart correlating the duration of prior arterial occlusion with the magnitude and duration of the decrease in blood flow after release of the occlusion (eighty-nine trials in seven subjects with thromboangiitis obliterans). Discussed in text.

SUMMARY

The resting blood flow in the horizontal position in the foot-leg of seven subjects with moderately advanced thromboangiitis obliterans was found to be within normal limits, as measured by the plethysmographic method.

The release of arterial occlusion in the thigh resulted in no significant increase in blood flow. No initial increase in limb volume and no significant cardiac acceleration followed the release of arterial occlusion in these subjects.

Heat or lumbar sympathetic ganglionectomy, alone or in conjunction with arterial occlusion, was no more effective in increasing the volume of blood flow than was simple arterial occlusion.

After the release of arterial occlusion, an initial decrease in blood flow was manifest. This was not prevented by local heat or by sympathetic ganglionectomy.

CONCLUSIONS

The maximal volume flow of blood in the foot-leg of the subjects with thromboangiitis obliterans whom we studied, consequent to the dilating procedures which were used, was determined largely by the narrowed arterial lumen produced by this disease. This maximum flow was less than that observed in normal persons. It may be reduced to the level of flow with which the normal limb is supplied at rest, or below this level. The distribution of the blood flow to the various parts of the foot-leg is not ascertained by measuring the total volume of inflow into the foot-leg.

Although there is no evidence to indicate that the dilating procedures which were used did not produce dilatation of the small vessels, it is possible that these procedures may evoke abnormal responses in this disease, both qualitatively and quantitatively.

The initial decrease in blood flow consequent to release of arterial occlusion may be caused by the above factor, by a peripheral vasoconstrictor effect of the ischemia, or, most likely, by a local constrictive response of the major vessels.

Since these last two factors may be active in the normal subject, this constrictive response need not of necessity be caused by thromboangiitis obliterans, but at least it becomes manifest in this disease.

The author acknowledges his indebtedness to Dr. L. N. Katz for his guidance. He is obliged to Dr. S. Perlow for permission to study his private patients and patients from the peripheral vascular clinic. He is very grateful, also, for the cooperation of these patients.

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DISSECTING ANEURYSM OF THE AORTA

CLAYTON D. MOTE, M.D., AND JESSE L. CARR, M.D.
SAN FRANCISCO, CALIF.

MORGAGNI¹ in 1760 first described a dissecting aneurysm of the aorta; he saw it "coming out under the external coats of the artery first by drawing it from the internal coats and then by raising it as a large kind of ecchymosis." Maunoir² in 1802 clearly described the mechanism of dissection by blood, and Laennec³ in 1826 first used the term "aneurysm dissequant." Peacock⁴ reported nineteen cases in 1843 to which he added sixty-one in 1863. Further excellent reviews and case reports were contributed more recently by Crowell,⁵ Moosberger,⁶ Wood, Pendergrass, and Ostrum,⁷ Etling⁸ and others. Gager⁹ in 1928 and Shennan¹⁰ in 1934 reported large series of cases. Because of this extensive literature, dissecting aneurysm of the aorta is today regarded as a rather common disease, and single cases are not especially noteworthy unless they present some unusual or interesting features.

In a five-year period, from 1933 to 1937, autopsies were done in sixty cases of dissecting aneurysm at the San Francisco Coroner's Office. An analysis of this volume of material is presented in this report. In addition are given the case reports of four patients with the antemortem diagnosis of dissecting aortic aneurysm. The second patient in this group was carried through pregnancy after the diagnosis had been made.

In 8,438 autopsies done at the San Francisco Coroner's Office during the five-year period upon which this report is based, dissecting aneurysm was found sixty times, or in 0.7 per cent. After deducting 3,099 cases of violent death, we find sixty instances of dissecting aneurysm in 5,339 cases, or 1.1 per cent. It is interesting to note that the incidence of ruptured heart as a cause of death in cases examined at the Coroner's Office is approximately the same, or 1.5 per cent.

The incidence of dissecting aneurysm as found in the Coroner's Office and as taken from hospital records varies considerably.

The higher incidence in coroners' records as compared to hospital records perhaps is explained partly by the fact that dissecting aneurysm of the aorta often occurs in patients who have had no previous symptoms of disease and who die suddenly.

From the Department of Medicine and the Department of Pathology, University of California Medical School, and the San Francisco Coroner's Office, San Francisco.
Received for publication June 23, 1941.

TABLE I
COMPARATIVE INCIDENCE OF DISSECTING ANEURYSM

	NO. OF AUTOPSIES	CASES	%
Shannon	1,922 in 24 years	11	0.56
Stanford	3,000 in 30 years	3	0.10
University of California	693 in 5 years	2	0.28
San Francisco Hospital	1,746 in 5 years	4	0.23
San Francisco Coroner's Office	8,438 in 5 years	60	0.7
(Nonviolent death)	5,339 in 5 years		1.1

The age, sex, cause of death, relation of exertion as known to the onset of the dissection are tabulated in Table II.

TABLE II

<i>Sex</i>		<i>Duration of Life in 60 Cases</i>	
Male	52	Found dead	18
Average age	58	Dead in 24 hours	39
Female	8	Dead in one month	58
Average age	63		
<i>Cause of Death</i>		<i>History of Exertion</i>	
External rupture	57	Severe	9
(Intrapericardial with tamponade 40)		Ordinary work	7
Heart failure	1	At stool	1
Obstruction of superior vena cava	1	Swimming	1
Rupture of associated aneurysm	1	External trauma	0*

*A total of 3,099 cases of violent death in 9,438 autopsies showed no evidence of dissecting aneurysm.

Because of the suddenness of death and the fact that these patients have not been attended, the clinical records and observations are often scant and unreliable. Therefore, when the clinical findings in the sixty cases of dissecting aneurysm are evaluated, it should be borne in mind that, although all the available material has been assembled, many details may be lacking.

Physicians attended the patients in only twenty-six cases of the series. The antemortem diagnoses made in these cases are given in Table III.

TABLE III

Cardiac conditions (heart failure, myocarditis, cardiac asthma, arteriosclerotic heart disease)	12
Coronary occlusion	2
Cerebral hemorrhage	1
Carcinoma of the stomach, hemorrhage	1
Aneurysm of the aorta	1
Chronic nephritis	1
Acute indigestion	1
Mediastinal tumor	1
Senility	1
Pulmonary hemorrhage	1
Lumbago	1
Dissecting aneurysm of the aorta	3

The clinical findings as reported in twenty-six cases of dissecting aneurysm that were seen antemortem by physicians are given in Table IV.

TABLE IV

Cardiac enlargement	10	Fever	4
Normal rhythm	25	Cough	3
Auricular flutter	1	Pleural fluid	2
Abnormal aortic sounds and murmurs	7	Basal râles	8
Aortic thrill	1	Hemoptysis	2
Aortic regurgitation	2	Albuminuria	8
Elevated blood pressure	7	Microhematuria	4
Normal blood pressure	19	Gross hematuria	1
Aortic dullness	2	Leucocytosis	4
Enlarged neck veins	2	Neurologic symptoms (i.e., reflex changes and weakness)	4
Occlusion of iliac arteries	2		

Electrocardiograms were taken in only two cases; in one, left axis deviation and flattened diphasic T-waves in Lead I occurred while in the other, that of a patient who was digitalized, auricular flutter with partial heart block was found. A study of the literature shows that marked electrocardiographic changes or notable variations from day to day do not occur in cases of dissecting aneurysm of the aorta. Roentgenograms were obtained in four cases. In the first case they showed no abnormality; in the second, cardiac enlargement with dilatation of the ascending and transverse arches of the aorta and pulmonary congestion were noted; in the third, the heart was enlarged and the thoracic aorta showed diffuse widening and elongation; in the fourth, there were two fusiform dilatations of the thoracic aorta, one on the ascending and one on the proximal descending aorta; the left ventricle was enlarged.

DIAGNOSIS

The number of patients in whom diagnosis of dissecting aneurysm of the aorta is made during lifetime is small because the condition is rare and because death often occurs before satisfactory observations can be made. Its presence is often overlooked in spite of our gradually accruing knowledge of the condition. If the aneurysm is recognized, proper supportive measures may be applied, and errors in diagnosis, which have led to operations such as exploratory laparotomy or other courses of treatment equally harmful, may be avoided.

In some cases the differentiation of a dissecting from a saccular aneurysm due to syphilis may be made from the history. The onset of the saccular aneurysm is usually gradual although its presence may be made known by acute symptoms. Generally, however, the saccular aneurysm is not acutely incapacitating, and it is usually due to syphilis. The roentgenograms of diffuse aortic aneurysm are often similar to those of the dissecting type.

Pain is one of the most constant findings in dissecting aneurysm, but it may be absent in some cases. It may vary from slight to excruciating in type. It is frequently described as "ripping" or "tearing" in

character. It may be persistent during the progression of the dissection, or it may be intermittent and less intense as the process becomes stationary. The location of the pain depends on the portion of the aorta in which the dissection is occurring. It may be in the chest, in the intrascapular region, in the lumbar region, in the abdomen, in the sacral region, or in the hips. In some cases the progress of the dissection may be observed by the changing location of the pain.

As the dissection progresses, intramural rupture of the vessels which arise in the aorta occurs. The dissection may extend also along the medial coats of these vessels. In either case there are obstructive signs in the peripheral circulation as a result of interference with the lumen of these vessels at the point of exit from the aorta. Neurologic manifestations are frequently seen. One of the most frequent symptoms is weakness of the lower extremities due to involvement of the branches of the aorta which supply the lower portion of the spinal cord.¹³ The paresis of the legs may be either transient or persistent. Urinary retention may occur due to sphincter disturbances. Syncope, convulsions, coma, and hemiplegia may result from interference with the cerebral circulation.

Any of the palpable peripheral vessels may be involved and at times difficulty in differentiation from an embolic or thrombotic occlusion of the vessel might arise, particularly when either iliac artery becomes occluded from a dissecting aneurysm of the abdominal aorta. The location of pain is an important factor in distinguishing between an embolic occlusion of the iliac artery and an occlusion due to a dissecting aneurysm. Embolic and thrombotic occlusion of the iliac arteries is accompanied by sudden severe pain which usually is in the calves of the legs and is due to ischemia of the leg muscles. In dissecting aneurysm of the abdominal aorta, the pain is usually sudden and acute in onset, is located in the abdomen or the back, and may radiate into the hips. The pain in this instance originates in the aortic wall and probably is due to splitting of the aortic coats. As the dissection proceeds and obstruction of the iliac arteries takes place, ischemic pain similar to that found in embolic or thrombotic occlusion of the arteries may occur in the lower extremities. In order to distinguish between these two conditions, emphasis is placed on the initial location of pain in dissecting aneurysm. When dissection occurs in the ascending arch, the pain is in the chest and back with perhaps occlusive signs in the arm or in the carotids accompanied by cerebral symptoms. The initial appearance of pain in the chest and the back is the important point in differentiation from embolism or thrombosis.

The pain in dissecting aneurysm may simulate and be indistinguishable from that found in coronary thrombosis. Of great help in differentiating these two conditions may be the almost simultaneous appearance of pain and peripheral vascular signs of an occlusive nature in dissecting aneurysm. There often are objective differences in the

carotid, brachial, radial, or femoral arteries, or such visceral manifestations as are seen in renal infarction with hematuria. Embolic phenomena in coronary thrombosis do not occur until sufficient time has elapsed for the formation of a myocardial infarct and a mural thrombus.

The sudden appearance of aortic murmurs and, not infrequently, of aortic regurgitation is of great diagnostic value. In most instances no actual involvement of the aortic valves is found. The insufficiency apparently is due to dilatation of the aortic ring as a result of the dissection of blood through the medial coat at the root of the aorta. As the blood approaches the aortic cusps, it interferes with the muscular elements that support the aortic ring which subsequently dilates.

PROGNOSIS

The prognosis in dissecting aneurysm of the aorta is grave. Various estimates of survival have been made. Crowell⁵ stated that 20 per cent of the patients have a chance to survive the initial episode. Weiss¹⁴ recently estimated that one in ten patients has a good chance to recover with development of a "healed" aneurysm. Thirty-eight of Shennan's¹⁶ 300 patients lived for two to thirty years. In our series of sixty cases, only two patients lived longer than a month after onset. The patient in Case 2 of the special case reports lived for two years and ten months after onset.

PATHOGENESIS

Although the opinions generally expressed in the literature as to the pathogenesis of the lesion may vary somewhat, they agree in certain details. First, it is held that the medial wall is weakened by a sequence of destruction and repair. The repair process consists of a light fibrosis with subsequent deposition of cholesterolin, fatty acid crystals, and calcium which are common to an arteriosclerotic process and unlike the strong, fibrous, vascularized tissue seen in syphilis. Second, the occurrence of a sudden rise in blood pressure is assumed. Third, it is held that a tear in the intima of the aorta may or may not occur. In the fifty-six cases of this series in which the intimal tear was described, the position was as follows: ascending aorta in forty-two, arch of the aorta in eleven, descending aorta just below the arch in three. In seven of the eleven cases of intimal tears in the arch, the aorta showed evidences of syphilis. In one case, two separate intimal ruptures were observed in the ascending portion of the arch, and in another the tear started in an atheromatous ulcer. The tears were from 2 cm. to 10 cm. in length and varied in shape, being crescentic, V-shaped, longitudinal, oblique, irregular, or transverse. The shape of the tear apparently had no relation to the extent of dissection or the condition of the intima, but simply took on the conformation of the weak medial portion when the dissection began. The external shape of the dissection between the layers of the aortic

wall was sheathlike in fifty, fusiform in six, and saccular in four cases. In most cases the separation of the coats of the aortic wall with extravasated blood extended from one-third to two-thirds of the aortic circumference. In one case, the aorta was completely encircled with blood, forming a so-called "tube-within-a-tube" arrangement.

Because of the common association of aneurysm of the aorta with syphilis, the question has been raised as to the relationship of syphilis to dissecting aneurysm. According to reports in the literature, aneurysm of the saccular type without dissection is due to syphilis in from 25 to 75 per cent of the cases, while most cases of dissecting aneurysm are due to arteriosclerosis uncomplicated by syphilis and only a small number to syphilis alone. In only two of the series of sixty cases of dissecting aneurysm was the diagnosis of syphilis made antemortem. In eleven cases, however, or 18 per cent, the presence of syphilis was proved post mortem either serologically or by tissue section. The cytologic criteria for the presence of syphilis were the microscopic pictures of perivascular infiltration of lymphocytes about the vasa vasorum, of scarring and vascularization of the media, and of mural fibrosis and wrinkling of the intima. According to these figures, the incidence of syphilis is somewhat higher than that found by Shennan, who reported its presence in 10 per cent of his cases of dissecting aneurysm. Arteriosclerosis was found in fifty-seven cases of the series. In most cases the arteriosclerosis of the aorta was far advanced, and generalized arteriosclerosis also was present. Nine of the eleven cases in which syphilis occurred presented a well-advanced arteriosclerosis equal in degree to that observed in many cases of dissecting aneurysm without evidence of syphilis. Thus, in only two cases of the entire series, or 0.3 per cent, a background of uncomplicated syphilitic infection of the aorta which resulted in sufficient damage to contribute to or cause a dissecting aneurysm was found. It has been suggested that syphilis uncomplicated by arteriosclerosis does not provide the necessary pathologic background for dissection of blood between the coats of the aortic wall.

Microscopically, the pathologic changes were largely those of an atherosclerosis. In addition to the usual deposit of fat, cholesterolin, calcium, and fatty acid crystals in the intima and media, evidences of inflammation in the intima and media were observed. These appeared in the form of lymphocytic nests, either isolated or perivascular, which were associated with intimal scarring by young fibrous tissue. These progressive pathologic changes preceded the aneurysmal dissection in varying degrees. The dissection itself usually started in small, localized areas of atheromatous degeneration and continued by splitting the lamina of the media by hydrostatic pressure from above. No evidence was found in any case of arteriosclerosis with occlusion of the vasa vasorum, and ischemia and degeneration of the aortic wall. There was no evidence of infarction of the aortic wall, either from embolism or

from sclerosis of the vasa vasorum, as suggested by Tyson.¹² In only one case sclerosis of the vasa vasorum was noted, and even then the changes were not sufficient to account for the areas of focal degeneration in the media. On the other hand, in several of our cases similar to those reported by Tyson, the intimal tear was not the starting point of the aneurysm and in four others the dissection was not accompanied by a tear. Furthermore, in two of our cases not included in this series, hematomas occurred in the aortic wall from rupture of the vasa vasorum in the media without extensive dissection and in the presence of an intact intima. In the one case a small organizing hematoma, about 2 cm. long, was found in the medial coat of the abdominal aorta. In the other, an organizing hematoma, about 12 cm. long, was noted in the media of the abdominal aorta. In both cases the lesions were found at autopsy and, while they were part of the process of generalized atherosclerosis, they had played no part in the clinical picture.

CASE REPORTS

The case reports of four patients with autemortem diagnosis of dissecting aneurysm of the aorta are presented.

CASE 1.—M. P., a man, aged 63 years, had dissecting aneurysm of the aorta extending from the ascending arch to the bifurcation of the abdominal aorta. The duration was fifty-four hours. There was terminal rupture into the pericardial cavity.

The patient was an Italian stevedore who did hard physical work until the onset of his terminal illness. His past history was irrelevant. He had no cardiovascular complaints.

On the morning of March 29, 1935, while at *stand*, he suddenly experienced weakness of the right leg which was followed almost immediately by severe substernal and interscapular pain. The paresis of the leg was transient, but the pain persisted. It was described as "tearing" in character and was extremely severe. It was most severe in the interscapular region and later extended into the lumbar region.

The patient was a well-developed and well-nourished man who was in considerable discomfort from pain at the time of examination. He had no fever. The important physical findings were limited to the cardiovascular system. The heart was slightly enlarged to the left. There was dullness in the second interspace to the right and the left of the sternum. The rhythm was regular; the pulse rate was 104 per minute. The heart sounds were *forceful* and of good quality. A loud to-and-fro murmur which was maximum at the aortic area was transmitted toward the apex. Peripheral signs of aortic regurgitation were present. The carotid pulsations were equal and *forceful*; the radial pulses were equal and Corrigan in type; and the femorals were equal. Both Traube's and Duroziez's signs were noted. Blood pressure in both arms was 100/80. The Wassermann reaction was positive.

The patient's condition remained the same for forty-eight hours, at the end of which time he experienced an exacerbation of severe substernal pain which had persisted since onset. He then began to show cyanosis of the face, neck, and upper extremities. The veins in the neck were distended. The heart sounds were diminished, and cardiac dullness increased to the right and left of the sternum. The peripheral signs of aortic regurgitation were no longer present, and the blood pressure fell to around 100/60 in both arms. The patient died about six hours after

this episode, which evidently marked the time of rupture of the aneurysm into the pericardium. He died fifty-four hours after the onset of the first symptom.

During the period of observation, which extended from shortly after the onset of symptoms until death, the patient voided only a few cubic centimeters of urine which consisted of almost pure blood. The clinical picture was typical of a dissecting aneurysm of the aorta with terminal rupture into the pericardial sac. The onset with transient neurologic signs, the character and location of the pain, the interference with renal circulation, and the presence of aortic regurgitation possibly of recent appearance indicated the diagnosis.

Autopsy.—Inasmuch as the important pathologic findings were in the heart and the aorta, the remainder of the autopsy findings are omitted.

The pericardial sac was dilated and of a peculiar purplish-blue color. It contained approximately 400 c.c. of partially fluid and partially clotted blood. The heart was slightly enlarged. A transverse tear was found in the posterior wall of the aorta approximately 6 cm. above the aortic ring. The blood had dissected from this point downward between the elastic laminae of the aorta into the pericardial cavity. Distal to the tear, blood had dissected its way between the central laminae of the aortic media for about half the circumference of the aorta on the right side. This area of dissection and splitting of the media extended down to and about the renal artery, and from this point blood had dissected upward to the right between the laminae of the renal artery. Some blood had escaped into the renal pelvis from a large infarct of the kidney. The dissection continued down to the bifurcation of the aorta where numerous thrombi were found. No re-entry of the aneurysm into the aortic lumen was present. Sections through the heart showed no pathologic changes in the endocardium, pericardium or valves, but did show a moderate sclerosis in the coronary system. No coronary thrombosis was noted. The intima of the aorta showed considerable thickening due to fibrous tissue and atherotic plaques along the entire course.

CASE 2.—R. B., a woman, aged 32 years, had dissecting aneurysm of the aorta. The duration was two years, ten months, and eight days. Onset was during pregnancy; a normal child was delivered at term by cesarean section.

The patient was first seen by her obstetrician, Dr. E. F. Anderson, on Oct. 1, 1937, when she consulted him for prenatal care. Her last menstrual period had been May 11, 1937, and her pregnancy had proceeded normally except for nausea.

Her past history was essentially negative. She had had no scarlet fever, rheumatic fever, tonsillitis, diphtheria, or pneumonia. Her cardiovascular system had been normal except for occasional "palpitation." She had been married for nine years and had had a previous normal pregnancy and labor in 1933. Except for the pregnancy (the uterus was the size of a four and one-half to five months' pregnancy) the examination was negative. No cardiac abnormalities were noted. The blood pressure in the left arm was 120/70.

On the evening of Oct. 1, 1937, while sitting in an automobile in front of her home, she experienced a sudden severe substernal pain. With assistance she was able to walk into the house. The pain was extremely severe and from the substernal area radiated upward into the neck and then downward posteriorly between the scapulae. At this point it remained and extended into the region of the xiphoid. It remained constant and severe for about thirty hours.

When the patient was first seen thirty hours after onset, she was writhing in bed with severe pain which radiated subinternally from the scapular region to the xiphoid. She was a tall, well-developed young woman. She was not in shock and did not have fever. The notable findings were limited to the cardiovascular system. A sharp systolic pulsation was noted in the suprasternal notch and extended well into the left carotid artery. The heart sounds were of good quality. A rough,

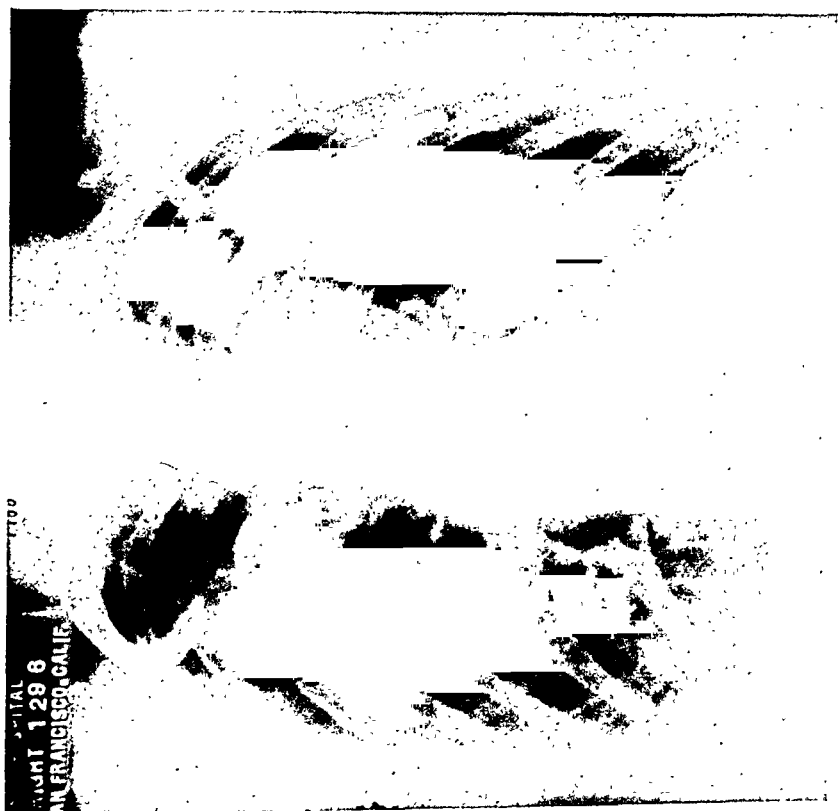
loud systolic murmur and a softer diastolic murmur were heard at the aortic area. The systolic murmur was loudly transmitted into the suprasternal notch and into the carotids. Examination of the peripheral pulses revealed the usual signs of aortic regurgitation in the left carotid, left arm, and lower extremities, and also Traube's and Duroziez's signs. The right arm and hand were cooler than the left, and the radial and brachial pulses on the right were smaller than on the left. Pulsation in the right carotid was markedly diminished, while in the left it was vigorous. Blood pressure was 130/0 in the left arm and 80/60 in the right arm; it was 160/0 in both legs.

Within a few days the pulsation in the suprasternal notch became more marked, and the aorta, which could be palpated here, was slightly tender. As time went on the pulsation in the left carotid diminished. The inequality in the radial pulses persisted; in time the right pulse became definitely retarded. Blood pressure was at all times about 120/30 on the left and 70/60 on the right. Since the dissection apparently did not progress further after the patient had been confined to bed at home for two and one-half months, she was allowed to be up and about. The first roentgen and electrocardiographic studies were made at this time (see Figs. 1 and 2).

Four months after the onset of symptoms, delivery was performed by cesarean section under spinal anesthesia (Feb. 2, 1938). The patient's postoperative course was uneventful. Until May, 1940, her condition remained about the same; although she was not completely well, she was able to be up and to attend to light household duties. During this period she had several transitory episodes of sudden weakness in the lower extremities. She also had transient periods of from five to fifteen minutes during which her visual acuity was markedly diminished. She became easily fatigued and always was conscious of palpitation. She had occasional "sticky" pains around the costal margins but never severe pain such as that which initiated the dissection. The aortic insufficiency persisted. Her heart gradually increased in size, but at no time did she show signs of congestive failure. Pulsation in the right carotid became almost imperceptible, and in the left carotid it was diminished. In February, 1940, roentgenograms showed increase in the size of both the aneurysm and the heart; also the electrocardiogram showed considerable changes (Figs. 1 and 2).

During the last three months of her life, the patient was confined to bed because of weakness and increasing bouts of pain. The pain was the same as that previously experienced and at times radiated also into the lumbar region and the right hip. Marked weakness developed in both lower extremities. No neurologic changes occurred other than hypoaesthesia over the distribution of the right femoral cutaneous nerve and diminution of deep reflexes in the lower extremities. At times the patient had great difficulty in emptying her bladder; urination finally became automatic, and the bladder was continuously distended. The pulsation of the abdominal aorta gradually became less forceful, and the aorta itself seemed tender to pressure. The other peripheral vessels showed no further changes. During the last month of life, the patient became very pale and somewhat cyanotic. She had periods of faintness, breathlessness, and weakness, and attacks of "suffocation." She also had some dysphagia, especially for liquids. However, congestive heart failure did not develop, and her lungs remained clear. Her condition became slowly but progressively worse. Her death was not marked by any dramatic event such as external rupture of the aneurysm. She died on August 8, 1940, two years, ten months, and eight days after the onset of the dissection.

The laboratory findings were not important. Numerous urine examinations were normal; two blood counts were normal, and the blood Wassermann reaction was negative.

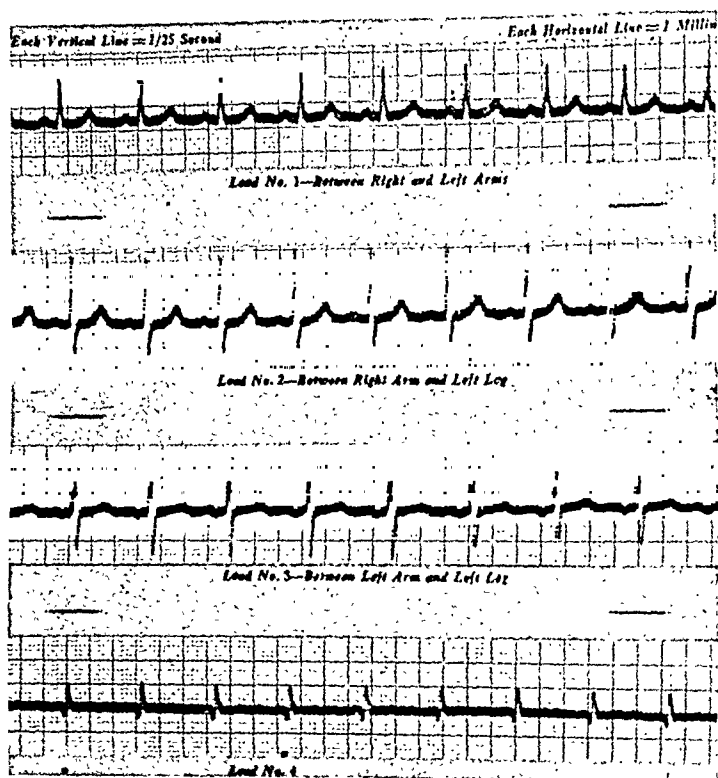


A.

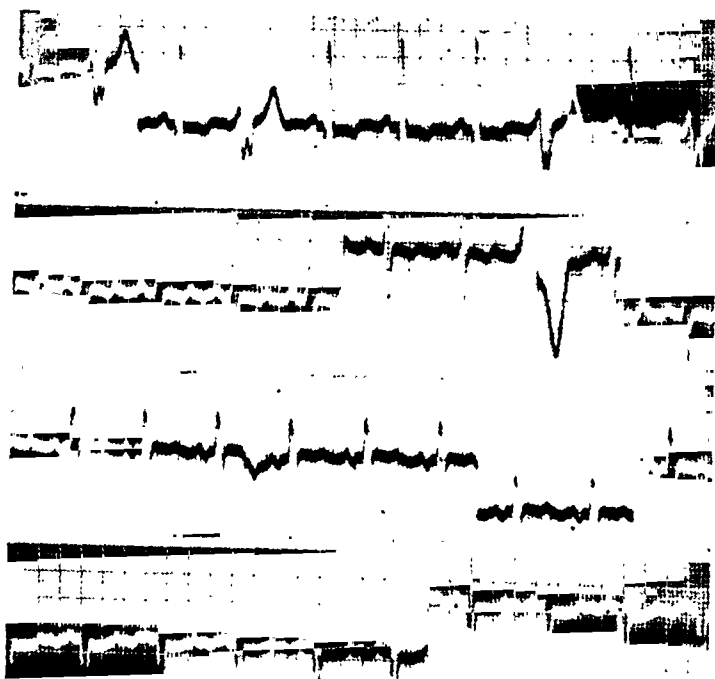


B.

Fig. 1.—Case 2. A. Two meter chest film two and one-half months after onset of the dissection. Note the uniform dilatation of the entire arch and upper thoracic aorta with elongation of the arch and beginning cardiac enlargement to the left. B. Two meter chest film twenty-seven and one-half months after onset of the dissection. There has been a marked increase in size of both aneurysm and the heart; the cardiac enlargement is on the basis of aortic regurgitation.



A.



B.

Fig. 2.—Case 2. A. Electrocardiogram two and one-half months after onset of the dissection. No abnormalities noted other than a left axis deviation. B. Electrocardiogram twenty-seven and one-half months after onset of the dissection. Changes are noted in the T waves in Leads I and II and also in the appearance of ventricular ectopic beats.

Autopsy.—No remarkable pathologic changes were found in any organs except in the heart and aorta.

The pericardial cavity contained clean visceral and parietal layers. There were only a few cubic centimeters of clear yellow fluid, but no free blood was found. The proximal 5 cm. of the aortic arch were dilated and formed a sacculum in the right and anterior aortic wall which projected forward and laterally to the right in a large, round knob about 8 cm. in diameter. This formation extended to the innominate artery and exerted considerable pressure upon it externally. In the anterior wall of the aorta, about 3.5 cm. above the aortic ring, a long, jagged, horizontal tear formed the entrance to an artificial channel which extended from this point down to the aortic bifurcation and had dissected into the left carotid artery. This channel in the aorta was crescentic on cross section; it extended through the middle of the elastic laminae of the media separating them widely, and from the front of the aorta around both sides to about 5 cm. from the midline posteriorly. In practically the same form it extended from the superior tear in the ascending aorta throughout the entire length of the aorta to the bifurcation. At that point it reentered the original aortic lumen through a horizontal tear in the anterior wall of the aorta just above the bifurcation. Thus, a second channel had been formed which extended from the ascending portion of the aorta to the bifurcation. The blood, which, in coagulating, at one time might have occluded this area, had been resorbed. The walls of the artificial channel were smooth and were lined with an adequate layer of endothelial cells. The blood had been circulating freely through this secondary channel. The original channel was patent; only its shape was changed and its caliber was reduced due to backward displacement of its anterior wall by the pressure of blood in the secondary lumen which lay anteriorly. Neither appreciable atherosclerosis nor thrombi were found in either of the channels. No lesions were found in the valves or muscle of the heart. The coronary system was patent.

Microscopic sections of the cardiac muscle showed medium-sized myofibrils separated by slight edema. The endocardium and pericardium were normal. The coronary system showed no appreciable sclerosis. In sections of the aortic wall the intima was flat and showed no thickening or infiltration with atheromatous deposits. In the media, however, the elastic laminae were deeply stained with eosin and showed an acidophilic character with some swelling of the individual elastic fibers. Between the elastic fibers and laminae a peculiar degenerative material was seen which stained blue with hematoxylin and offered an easy plane for cleavage by manual dissection. No scarring or vascularization of the media was noted. The adventitia was normal and contained numerous patent vasa vasorum which showed no sclerosis or endarteritis and carried adequate circulation into the aortic wall. In some sections large arterioles and venules extended into the media, and about several of these there were free erythrocytes.

CASE 3.*—J. K., a man, aged 54 years, had dissecting aneurysm of the aorta. The duration was twenty-nine hours. No autopsy was done.

This patient was seen for the first time at noon on Oct. 19, 1938. He had been well and working at his regular occupation of fireman until the previous day. At about eleven o'clock he had felt sudden severe mid-abdominal pain which had been followed by severe pain, tingling, and weakness in the left leg. He had not vomited. The pain had been paroxysmal in character and had not radiated into the back.

At time of examination the patient was in extreme pain. He was cold, cyanotic, and sweaty. The important findings were limited to the cardiovascular system. The heart sounds were good. Systolic murmurs were heard at the base and apex.

*By courtesy of Dr. E. L. Bruck.

The rhythm was regular, and pulse rate was 96 per minute. Pulsations in the left carotid artery were less forceful than in the right. The left radial pulse was barely palpable, but the right was normal. The right femoral pulse was normal, but the left was absent. The left leg was cold and blanched, and no pulses were elicited in the left foot.

Within one-half hour the pulsations in the left carotid, brachial, and radial arteries could not be felt. Systolic and diastolic murmurs were heard over the entire precordium. Blood pressure was 115/74 in the right arm. Severe pain continued for twenty-four hours. Gradually the pulses in the right carotid and brachial arteries became smaller, and the patient died in circulatory failure about twenty-nine hours after the onset of symptoms. Death may have been the result of a rupture into the pericardium or possibly of obstruction of both carotids. Permission to perform an autopsy could not be obtained. The onset and progress of the illness in this case were typical of a dissecting aneurysm of the aorta.

CASE 4.*—D. Mc., a man, aged 72 years, had dissecting aneurysm of the aorta. The duration was three hours. There was terminal rupture into the pericardial cavity.

This patient had been observed for a number of years. He had had rather extensive vascular changes due to arteriosclerosis, and his blood pressure usually had been about 180/100. His past history otherwise was not relevant to his terminal illness.

On May 2, 1936, while the patient was walking across his room, he had a sudden severe pain at the lower end of the sternum. The pain was felt through to the back. Later, pain developed in the right leg. When he was first seen, he was in shock, had vomited, and was cold, sweaty, and pale. The pulse rate was 100 per minute. The heart sounds were distant, and a soft systolic murmur was heard at the apex. There was severe pain in the right leg which was cold. The right femoral pulse was absent. The left femoral pulse and the left foot pulses were present. The patient's condition became progressively worse. A loud systolic and diastolic bruit developed over the upper precordium. The blood pressure could not be obtained in either arm. The patient died about three hours after onset of the dissection.

Autopsy.—The aorta showed marked atheromatous changes. The dissecting aneurysm extended along the entire vessel from the aortic ring to the bifurcation. It communicated with the lumen through a small intimal tear just above the bifurcation of the abdominal aorta. There were no other intimal tears. Death had resulted from rupture of the aneurysm externally into the pericardial cavity at the root of the aorta just inside the pericardial reflection.

COMMENT

Little has been added to the picture of dissecting aneurysm of the aorta since the report of Peacock,⁴ who was the first to put our knowledge of this condition on a firm foundation with a satisfactory and well-reasoned account of the disease. He recognized that a lesion of the media formed the background for the dissection, but he considered the rupture of the intima as the initial step in the process. Shennan,¹⁰ in his comprehensive review of 300 cases with especial attention to the pathologic aspects of the disease, also concluded that the essential change was in the media. He found that in most cases the media gave way

*By courtesy of Dr. E. L. Bruck.

before the intima and concluded that the immediate or exciting cause was a sudden increase of blood pressure due to physical or mental strains and stresses.

Our series of cases does not differ greatly from those previously reported. As has been noted, the important change is medial degeneration with weakening of the elastic laminae of the wall of the aorta. Hemorrhage from the vasa vasorum into the diseased media may occur; in some cases it is extensive and not associated with an intimal tear. For this reason Eppinger¹⁶ (1887) called the lesion an intramural hematoma of the aorta, a term which we believe is appropriate in some instances. The base of an atheromatous ulcer is rarely the site of the intimal rupture. As a rule, the location of the tear in the intima bears no relation to disease of the intima but rather depends on underlying medial changes in the elastic lamina and on the dynamics of the aortic pulsations.

Although Shennan stressed the importance of the systolic blood pressure, he considered the diastolic recoil in the ascending aorta a more important factor in the intimal rupture. Elliotson¹⁷ (1830) stated that the occurrence of a rupture was not necessarily dependent on an elevation in blood pressure but that it could be adequately explained on the basis of the degenerative lesion of the media. It is interesting to note that in our series the blood pressure was elevated in seven and normal in nineteen of the cases in which it was recorded. In Case 2, the blood pressure was normal a few hours before the onset of the dissection and on many subsequent occasions the systolic pressure was always the same. We believe this supports the suggestion that an elevated blood pressure is not essential for the formation of a dissecting aneurysm.

We have noted two cases in which a small dissecting aneurysm was found in the wall of the abdominal aorta. No intimal rupture occurred. The aneurysms were silent and took no part in the clinical picture. It is probably significant that in both cases the aneurysms were in the abdominal aorta. In the ascending aorta the same degree of medial change with hemorrhage and degeneration would most likely have led to an intimal tear followed by the usual course of a dissecting aneurysm. Medial change, systolic stretching, and diastolic recoil seem to be the conditioning factors for intimal rupture in the ascending aorta.

In only two of the sixty-four cases presented in this report, uncomplicated syphilitic aortitis occurred. In the nine cases in which the presence of syphilis was proved either serologically or microscopically advanced atherosclerosis consistent in degree with that found in cases of dissecting aneurysm without syphilis was also present.

In thirty cases the patients were seen by a physician before death occurred; in the remaining thirty-four cases the patients died so suddenly that medical attendance was impossible. In seven cases diagnosis was made before death.

Case 2 was of special interest because the dissection developed during pregnancy. The relation of pregnancy to dissecting aneurysm is not yet clearly understood. In a review of the English literature, McGeachy and Paullin¹⁸ reported twenty-four cases in females, six of whom were pregnant. This incidence is high, and it is interesting to speculate on the relationship of pregnancy to the medial changes that lead to dissecting aneurysm.

A number of recent contributions have stressed the importance of cystic necrosis of the aortic media to dissecting aneurysm of the aorta and also to spontaneous rupture of the aorta. The pathologic picture of medionecrosis aortae idiopathica cystica was first brought out by Erdheim¹⁹ and more recently in an excellent review by Roberts.²⁰ The high incidence of this medial change in pregnancy is noteworthy. In Case 2 of this report the medial change was similar to that described by Erdheim although no true cystic areas were observed. In most of our series the degenerative medial change was observed in varying degree and has been considered an atheromatous type of degeneration.

The prognosis in dissecting aneurysm is generally poor. However, an extensive dissection may be repaired either by organization and fibrosis of the aneurysm and the clot in it or by endothelialization of the artificially formed tube which, following lysis and resolution of the clot, may be converted into a physiologic conductor of a fluid stream.

CONCLUSIONS

Sixty-four cases of dissecting aneurysm of the aorta are presented. This condition occurs primarily in arteriosclerosis and exceptionally in syphilis or in a combination of these. Syphilis is found in most cases of saccular aneurysm but in only a small number of the cases of dissecting aneurysm of the aorta. In this series of sixty-four cases, it was found without atherosclerosis in only two.

The point of initiation is a ruptured vas vasorum in a weakened media which forms a small spreading hematoma. The process usually occurs without demonstrable pathologic changes in the vasa vasorum but rather as a disease of the aortic media only. In rare instances the point of initiation is a tear in the intima at the site of atherotic deposits. The dissection may remain static; on the other hand, it may rupture either through the adventitia, with hemorrhage into the adjacent structures, especially the pericardial cavity, or back into the aortic lumen.

Dissecting aneurysm of the aorta is not as uncommon as hospital records indicate. Due to its rapid and fulminating character, it frequently results in sudden death so that hospitalization and medical study are precluded. Furthermore, statistics have been meager because of the incomplete or negligible records of medicolegal and coroners' offices.

External trauma is not a predisposing factor to the production of a dissecting aneurysm.

Elevation in blood pressure is not an essential factor in this condition.

The antemortem diagnosis of dissecting aneurysm of the aorta is made with increasing frequency and will be made even more often if the not uncommon occurrence of the disease is kept in mind and its characteristic findings are brought out by careful clinical observation.

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DISCUSSION

DR. AARON ARKIN, Chicago.—I have seen a number of cases of dissecting aneurysm of the aorta and wish to make a few remarks about the pathology and clinical picture.

Most of the patients were young adults with marked hypertension. The first case which I saw some years ago in Vienna was one reported by Professor Erdheim in his fine work on the histopathology of the aorta in these cases. He described a peculiar type of medionecrosis, a non-inflammatory necrotizing process affecting the media, and producing mucoid cystlike areas of degeneration. He called this medionecrosis aortae cystica. Similar small foci have been found in the aorta in routine examinations.

One patient was a young engineer 30 years old with marked hypertension. He developed terrific substernal pain and died in a few hours. The necropsy revealed a supravalvular tear, with hemorrhage into the pericardium and heart tamponade. The aorta revealed a medionecrosis.

A few months ago I saw a young physician of 40 who had essential hypertension. While sitting in the hospital office, he developed a severe pain in the heart region which soon radiated to the back of the chest between the shoulder blades. The next day the pain was in the upper abdomen. At the onset he could neither stand nor lie down, and lay in a chair in a semirecumbent position.

The electrocardiogram was practically normal. His hypertension, profound shock, agonizing pain with radiation down the back, and normal electrocardiogram suggested a dissecting aneurysm.

The disappearance of the pulse in an arm (usually the left) or in the left carotid with the above clinical picture lends support to the diagnosis. The clinical picture may resemble an acute abdomen, perforated ulcer, or acute pancreatitis, as well as myocardial infarction. X-ray examination may be of value when a widening of the aortic arch, innominate, or left carotid shadow appears. On the other hand, there are cases of slow development with few symptoms; these patients may live for months or years.

DR. WILLIAM B. KOUNTZ, St. Louis, Mo.—I should like to say a word about hypothyroidism and this condition. When the fever of taking out thyroids for the relief of heart disease was at its height, in our clinic, four cases had thyroids removed. All of these patients were young individuals and had severe hypertension and impending cardiac failure.

The first two patients died with ruptured aortas six months after the operation. Because of this, the other two were put on thyroid. One, the third case, lived for two and a half years, and finally, on her own initiative discontinued thyroid treatment; she died six or eight months later, with a ruptured aortic aneurysm. The fourth patient is still living under pressure of thyroid therapy.

Our pathologist, Dr. Robert Moore, diagnosed the slides as being, as Dr. Arkin has suggested, Urdheim's disease or a cystic necrosis of the aortic muscle.

I should like to ask the essayist if any of these cases, especially the cases he had a chance to follow, showed any hypothyroidism clinically.

It is possible to demonstrate muscle degeneration in animals by taking out the thyroid. I had never seen ruptured aorta in animals, but aortic degeneration occurs. Dr. David Barr has reported a case of clinical myxedema since our experience with induced hypothyroidism in May with a basal metabolism of minus 36. In his case there was degeneration of the aortic muscle and also of the smooth muscle of the intestinal tract.

DR. EUGENE S. KILGORE, San Francisco.—Dr. Moté and Dr. Carr have done well to introduce the subject of dissecting aneurysm, which, as they show, is less rare than is commonly supposed. The condition has only recently begun to be diagnosed clinically, and certain details of the clinical picture still need clarification. Two such details are especially worthy of attention by those who report cases.

One is the question of strain as a precipitating cause, which will certainly require medicolegal consideration. Among the cases thus far reported, physical activity has immediately preceded the pain with sufficient frequency to be probably significant. But the exertion has often been mild and may be overlooked without careful questioning. In several reported cases it was straining at stool; in a pregnant woman it was the act of stooping; in a patient of mine it was the act of reaching high up to insert an electric bulb; and in another it was leaning over a table. Middleton reported the case of a man in whom pain began suddenly while

he was removing an overcoat. Shennan described one whose attack began while he was swinging onto a bus, and another who was tolling a bell. All are instances of mild exercise, but suggest contortion of the thorax as a precipitating cause of dissection. Other histories, like that of Dr. Mote's patient, clearly exclude such a factor, but the bulk of the published case reports leave the question of strain unanswered.

The other detail needing more exact description is the character of the pain as distinguished from its location, especially the presence or absence of throbbing. This was denied by two patients recently seen and was described by another of mine and by a patient of one of my colleagues. But the information was obtained only by direct questioning, and it seems not improbable that throbbing has often been present when not mentioned in case reports. For it is easy to understand a rhythmic aggravation of pain when successive pulse waves are splitting the aorta bit by bit or stretching the newly formed aneurysmal cavity, and it is possible that throbbing pain will be found to be a significant symptom of advancing aortic dissection.

DR. MAURICE S. JACOBS, Philadelphia.—A week ago yesterday, I had the sad duty to go to the funeral of my cardiac chief in Philadelphia, who died of a ruptured dissecting aneurysm. We had known for about two years that he had dissecting aneurysm following hypertension of many years' duration. He had been invalided because of progressive cardiac anoxemia, with minor episodes that from time to time suggested acute myocardial infarction.

The interesting thing was the unusual site of that rupture, which was posteriorly, and into the esophagus, resulting in massive hemorrhage. As fast as he could get blood by transfusion he lost it. He finally died five days after the sudden rupture which occurred while he was absolutely quiet in bed.

DR. CLOUGH T. BURNETT, Denver Colorado.—Those discussing the paper have not mentioned the recurring type of pain which occurs in these people who do not die in the initial attack.

A restaurant man in the late fifties, who had been known to be moderately hypertensive, attempted to carry a light coffee urn. He had a terrific pain, was in shock, and was considered to be in an attack of coronary thrombosis.

He was in such extreme shock that the initial examination was limited mainly to the heart. His pain disappeared for probably six or eight hours, but recurred over a period of about five days. Each time the pain was a little more severe. With repeated bouts of pain, there was at no time any E.K.C. evidence of coronary occlusion. About the third day, when I saw him in consultation, it was noted that he had a dullness in the left chest, without associated symptoms or signs that would indicate pneumonia. He did not have temperature elevation, but some leucocyte increase. X-ray examination suggested left upper lobe pneumonia.

In an attempt to determine what this dullness might represent, a needle was introduced and pure blood was obtained. He died about five days after the onset. Autopsy showed a dissecting aneurysm probably 8 cm. in length, finally perforating into the left pleura, with an enormous amount of blood in the left upper pleura.

DR. DREW LUTEN, St. Louis.—Although at present dissecting aneurysm of the aorta is regarded as almost invariably fatal, and it is indeed almost impossible to make an unequivocal diagnosis without autopsy, yet in view of the fact that here and there cases are observed in which the patient later is shown to have survived, the question must arise whether future years will not witness a considerable increase in the number of patients who do not succumb.

While one could hardly expect the mortality in dissecting aneurysm to be other than very high, yet subsequent years may in some degree duplicate the history of coronary thrombosis in which earlier conceptions of the mortality have had steadily to be revised downwardly.

In the case with restricted blood flow in the renal artery I am not sure whether Dr. Mote stated the blood pressure. I should like to ask him what the blood pressure was in that case.

DR. HERMAN E. PEARSE, Rochester, N. Y.—This discussion has pertained to dissecting aneurysm in a diseased arterial wall. I merely wish to say that it is possible with traumatic rupture of the aorta to anticipate a different course of events and perhaps a better prognosis. The basis for this statement is from the observation in aortic surgery that it is almost impossible to keep a small wound of the aorta open long enough to have extravasation of any magnitude. It is impossible to produce dissecting aneurysm in a dog because of the rapid healing of the vessel.

In patients whom I have seen with apparent dissecting aneurysm due to traumatic rupture of the aorta there has been no sign or symptom of difficulty from the lesion. One individual lived a week and then died of pneumonia in a traumatized lung; at post-mortem examination his aortic lesion was rapidly healing. Thus in the healthy, undiseased aortic wall, one may anticipate a picture simulating dissecting aneurysm but having a different course.

DR. T. J. DRY, Rochester, Minn.—I wish to add to the discussion one symptom or group of symptoms to which no reference has been made thus far, namely, those symptoms referable to the central nervous system. These consist of transitory weakness and paresthesia noted in the upper extremities. These are due to temporary interference with the blood supply to the spinal cord. It will be remembered that the spinal cord receives part of its blood supply from the intercostal vessels and during the dissection of the aorta these may be interrupted. At a later date the same evidence may occur at lower levels with symptoms corresponding to the spinal segments involved. This group of symptoms may be very helpful in the diagnosis of some of these cases.

DR. CLAYTON D. MOTE, San Francisco, Calif.—I am, indeed, grateful for the discussion. Many points are brought out that have been impossible for me to mention this afternoon and time will not allow detailed discussion now.

Dr. Yater brings up a practical point in differential diagnosis. I believe the location of the initial pain is very important in the differentiation of saddle embolus and dissecting aneurysm of the abdominal aorta. The pain of saddle embolus is in the legs, because of ischemia. The initial pain in a dissecting aneurysm arises in the wall of the aorta and appears in the back, abdomen, or thorax. As the dissection progresses and occlusion of an iliac artery subsequently occurs, pain appears in the legs and is indistinguishable from that of a saddle embolus.

We have not noted the association of myxedema and dissecting aneurysm as mentioned by Dr. Kountz. One wonders about a possible relation to cholesterol metabolism.

THE INCIDENCE OF HEART DISEASE IN MEXICO

A STUDY OF 2,400 CASES OF ORGANIC HEART DISEASE

IGNACIO CHÁVEZ,* M.D.

MEXICO CITY, MEXICO

SEVERAL statistical studies on heart disease have been published recently. Those from the United States, England, Czechoslovakia, and Argentina are particularly extensive and interesting. They inquire into the real importance of the different causes of organic disease of the heart and are intended to help the physician make an etiologic diagnosis in each case and to learn something about the prevention of heart disease. In order to appreciate the importance of the many possible causes, it would be very helpful if all countries would contribute their own statistics. The significance of factors such as race, climate, kind of work, and living standards, in increasing or decreasing the effect of universal causes, would thus be made apparent.

Mexico has not yet produced such a report, and this paper attempts to fill the gap by presenting the results of my personal experience. As will be seen, many of my data are similar to those from other countries, but some are entirely different, particularly with respect to diseases which affect the Indian race.

MATERIAL

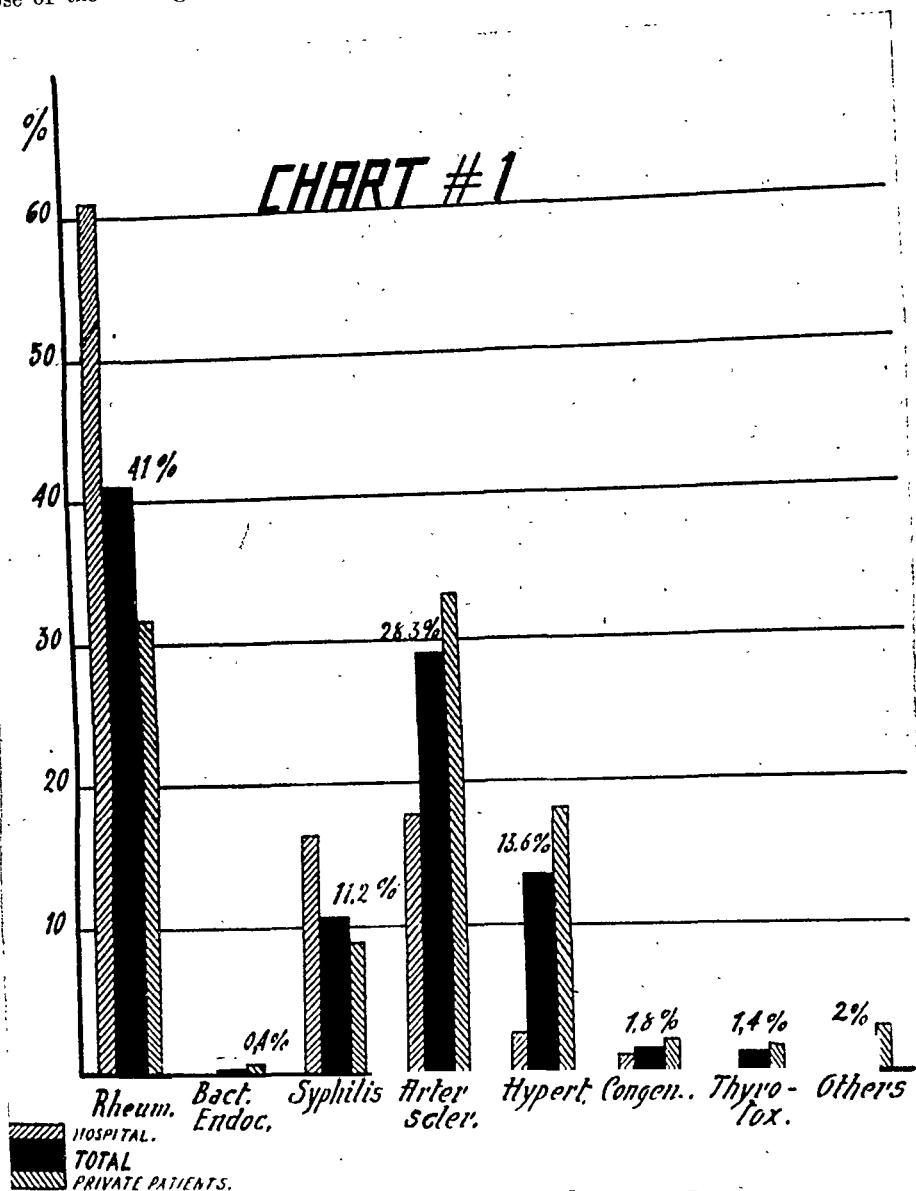
I have taken 726 cases from the cardiological service of the General Hospital. These patients were admitted during the last ten years. They were examined clinically, roentgenologically, and electrocardiographically, and laboratory studies were made in an attempt to ascertain the etiology in each case. To these I have added 1,674 private patients who were examined in the last five years; practically all of them were subjected to the same kind of study. Occasionally, in cases in which the diagnosis seemed obvious, no laboratory data were obtained. All of the 2,400 patients had demonstrable organic heart disease, except those with hypertension and thyrotoxicosis, who, for obvious reasons, were included. Patients with "functional" or neurotic cardiac complaints, who, as is well known, never develop heart lesions, were intentionally excluded.

In evaluating the results, it is important to note that the hospital patients were from a charity ward, and belonged to a very low income group; they were of mixed Indian and white blood (mostly Indian), or pure Indian. Some were farmers and others were city laborers; all lived under poor hygienic conditions. The private patients, on the other hand, were a heterogeneous group of pure whites and mixed

Presented at the seventeenth meeting of the American Heart Association, Cleveland, Ohio, May 30, 1941.

*Professor of Medicine, University of Mexico. Physician in Charge of the Cardiological Service, General Hospital.

racess of all kinds. Some were intellectuals, and others were manual laborers from the city and country. Their economic status and living conditions were better than those of the other group.



*Incidence of cardiopathies in Mexico.
Study of 2 400 cases of organic diseases*

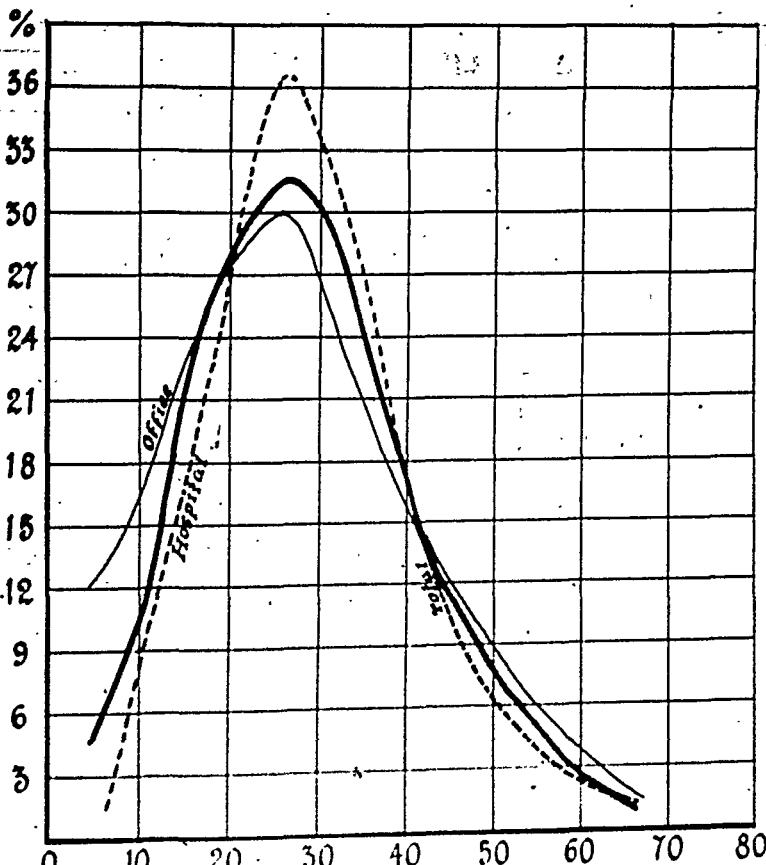
Table I and Chart 1 summarize the incidence of the various kinds of heart disease. The distribution in the two groups is somewhat different, particularly with respect to rheumatic heart disease and hypertension. It will be seen that the former was twice as common among the hospital patients, whereas the incidence of the latter was seven times greater among the private patients. This deserves further discussion.

TABLE I

	PRIVATE PATIENTS	PER CENT	HOSPITAL PATIENTS	PER CENT	TOTAL	PER CENT
Rheumatic heart disease	539	32.1	447	61.5	986	41.0
Bacterial endocarditis	9	0.5	-	-	9	0.4
Syphilis	147	8.8	123	16.9	270	11.2
Arteriosclerosis	551	32.9	128	17.6	679	28.3
Hypertension	309	18.4	19	2.6	328	13.6
Congenital heart disease	34	2.0	9	1.2	43	1.8
Thyrotoxicosis	35	2.0	-	-	35	1.4
Miscellaneous (cor pul- monale, anemia, cause not ascertained)	50	3.0	-	-	50	2.0
	1,674	99.7	726	99.8	2,400	99.7
Private patients						1,674
Hospital patients						726
Total						2,400

CHART # 2

Rheumatism.



----- Hospital : 447 cases - 61.5% in a group of 726 patients (Ill...187 W...260)
 ——— Office : 539 " - 32.0% " " " " 1674 " (Ill...219 W...320)
 ——— Total : 986 " - 41.0% " "total " 2400 " (Ill...406 W...580)

RHEUMATIC HEART DISEASE

The incidence of rheumatic heart disease in the 2,400 cases was 41 per cent, which is about the same as that reported by White and Jones,¹ in Boston (39.5 per cent), Wyckoff and Lingg,² in New York (42.7 per cent), Coombs,³ in England, and Brumlik,⁴ in Prague (40.5 per cent), but is lower than that reported by Ormhaug, in Norway (50.8 per cent). However, it is significantly higher than that encountered by Cossio,⁵ in Argentina (17.9 per cent, leaving out "functional" heart disease), and nearly four times as high as that reported from Texas by Schwab and Schulze⁶ and Stone and Vanzant⁷ (10 per cent in the white race and 3.6 per cent in Negroes). This incidence of 41 per cent, which is approximately as high as the highest in the world, destroys the myth that rheumatism is a rare disease in tropical or semitropical countries.

The incidence of rheumatic heart disease among the hospital patients was enormous (61.5 per cent); I know of no higher figure. It indicates not only a relative, but also an absolute, increase in the prevalence of the disease. The relative increase resulted from the scarcity of hypertension in the hospital group. When the latter is excluded, all of the others increase, but, even so, the incidence of rheumatic heart disease is disproportionate. The reason is not clear, but one wonders whether racial predisposition, poor hygiene, and the prevalence of chronic tonsillar infections among hospital patients may be factors.

The sex incidence among the hospital patients (males, 187; females, 260) and private patients (males, 219; females, 320) was exactly the same (males, 41 per cent; females, 59 per cent). Chart 2 shows that the peak of incidence occurred in the third decade.

CARDIO-AORTIC SYPHILIS

Chart 3 shows that the incidence of syphilis was about twice as high among the hospital patients (16.9 per cent) as among the private patients (8.8 per cent). The mean incidence (11.2 per cent) is higher than that in the northern part of the United States (2 to 7 per cent), Czechoslovakia (4.1 per cent), Argentina (6 per cent), and England (6.5 per cent), and lower than that in the southern part of the United States, where it is 15 to 31 per cent among Negroes. In Mexico, as elsewhere, males predominate in a proportion of about 3 to 1. The peak of incidence occurred in the fourth and fifth decades.

Of these 270 patients, 60 per cent had aortitis and valvular lesions, 6.2 per cent had aortic aneurysms, and only 72 per cent gave positive serologic reactions. These figures are similar to those which emerged from my analysis,⁸ several years ago, of 132 cases of syphilitic aortitis.

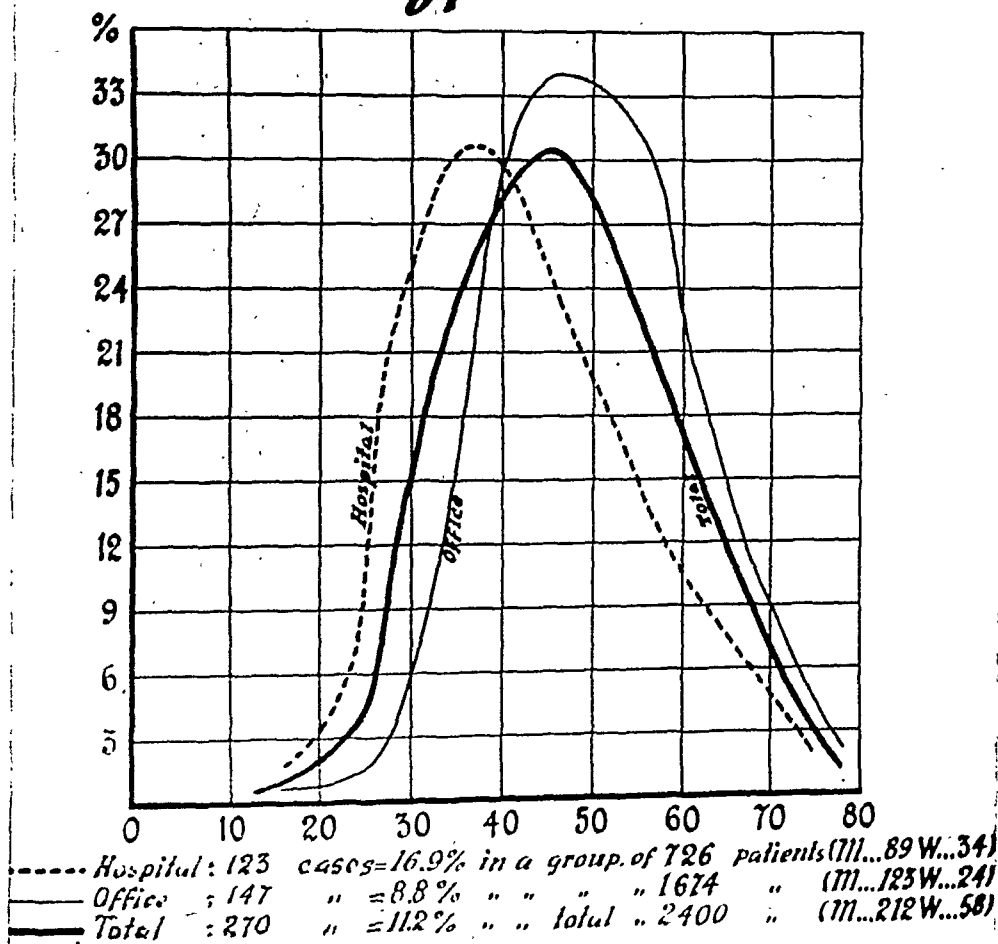
HYPERTENSION

Chart 4 shows the incidence of pure hypertension, unaccompanied by demonstrable arteriosclerosis or angina pectoris. The striking difference,

previously mentioned, between the private patients and hospital patients (18.4 per cent and 2.6 per cent, respectively) does not tell the whole story. It is well known that patients with hypertension who have no symptoms of coronary disease or of arteriosclerosis in other organs are not likely to be hospitalized. Furthermore, we meet with the difficulty in classification which was so well pointed out by White and Jones,¹ namely, that the patients with hypertension and arteriosclerosis have to be included with the pure hypertensives. Therefore, to the 328

CHART # 3

Syphilis.

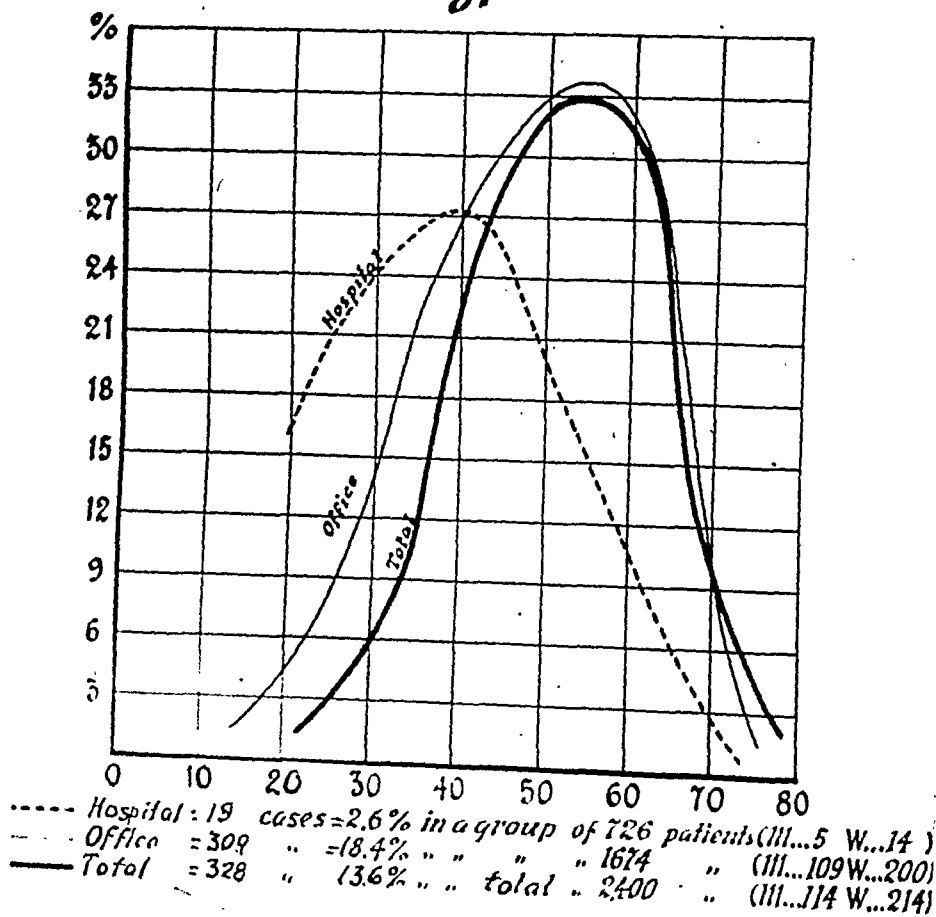


cases of pure hypertension we must add 343 of the "hybrid" group, which makes a total of 671 cases of hypertension, or 27.9 per cent of the total. However, when this is done in the hospital group, we still have only 7.3 per cent, which is one-fifth of the incidence among the private patients. Such a disproportion does not exist among other etiologic factors, nor in other countries or races. On the contrary, among the Negroes of Texas, Stone and Vanzant⁷ and Schwab and Schulze⁸ found

that the incidence of hypertension ranged from 50 to 57 per cent, and that malignant hypertension was unusually common.

Among our Indians the situation is just the opposite. I have said that our hospital population is made up of mixed-blood "mestizos" (who are mostly Indian) and pure Indians. Their food and hygienic conditions are poor, but in this instance these factors do not seem to play a role. I am inclined to think that there is a racial factor which operates through a nervous mechanism. For centuries the Mexican

CHART # 4 *Arterial Hypertension*

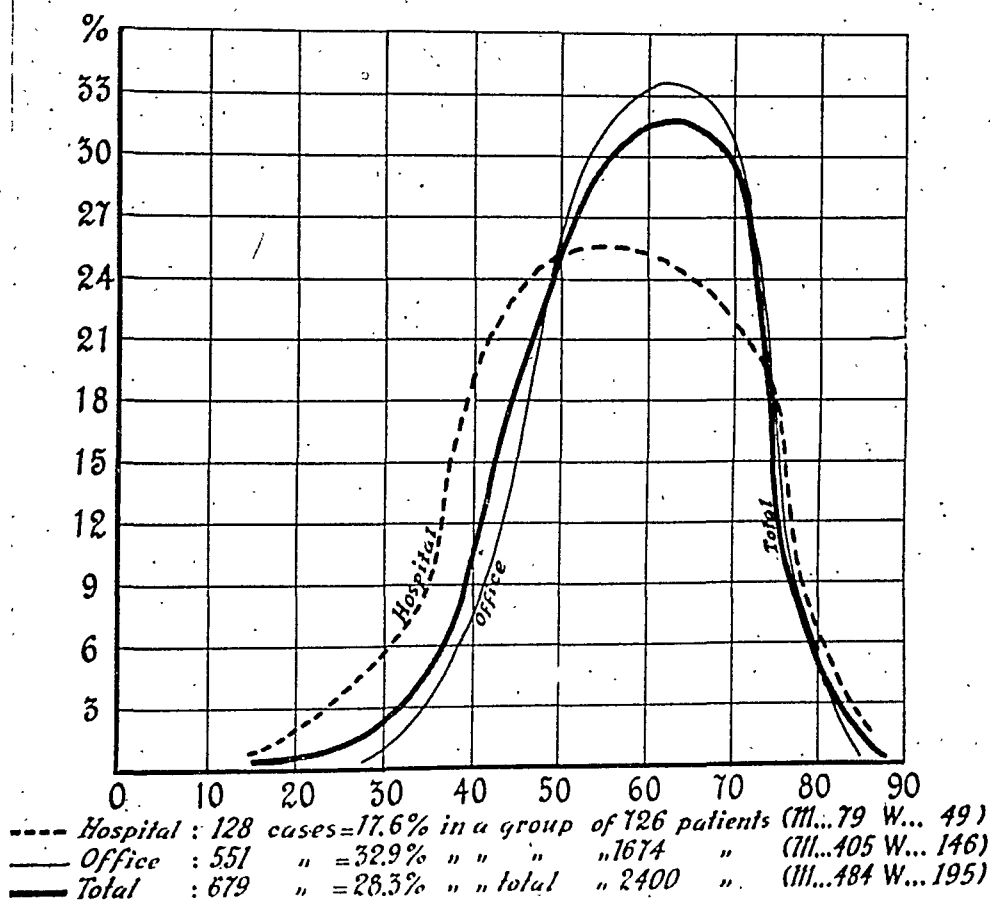


Indian has lived a slow and unharassed life. His manual labor may sometimes be strenuous, but he knows nothing of uneasiness or anxiety. His philosophy of life is conformist, if not fatalistic. He has a well-balanced nervous system which protects him from the ordinary impacts of life, and he knows nothing of psychasthenia. What we call civilized living either does not reach him, or, if it does, fails to traumatize his mind. This may explain his relative freedom from hypertension, angina

pectoris, and coronary occlusion. Those who think that a nervous mechanism is an important, if not the sole, factor in the pathogenesis of these diseases may possibly find support for their point of view in this peculiarity of the Mexican Indian.

It would be interesting to know whether the Indians of Central and South America—and perhaps those of the United States—enjoy the same immunity, and to follow the Mexican laborer who stays in the United States for a long time, to see how he fares with respect to hypertension, angina pectoris, and myocardial infarction.

CHART # 5 Arteriosclerosis.



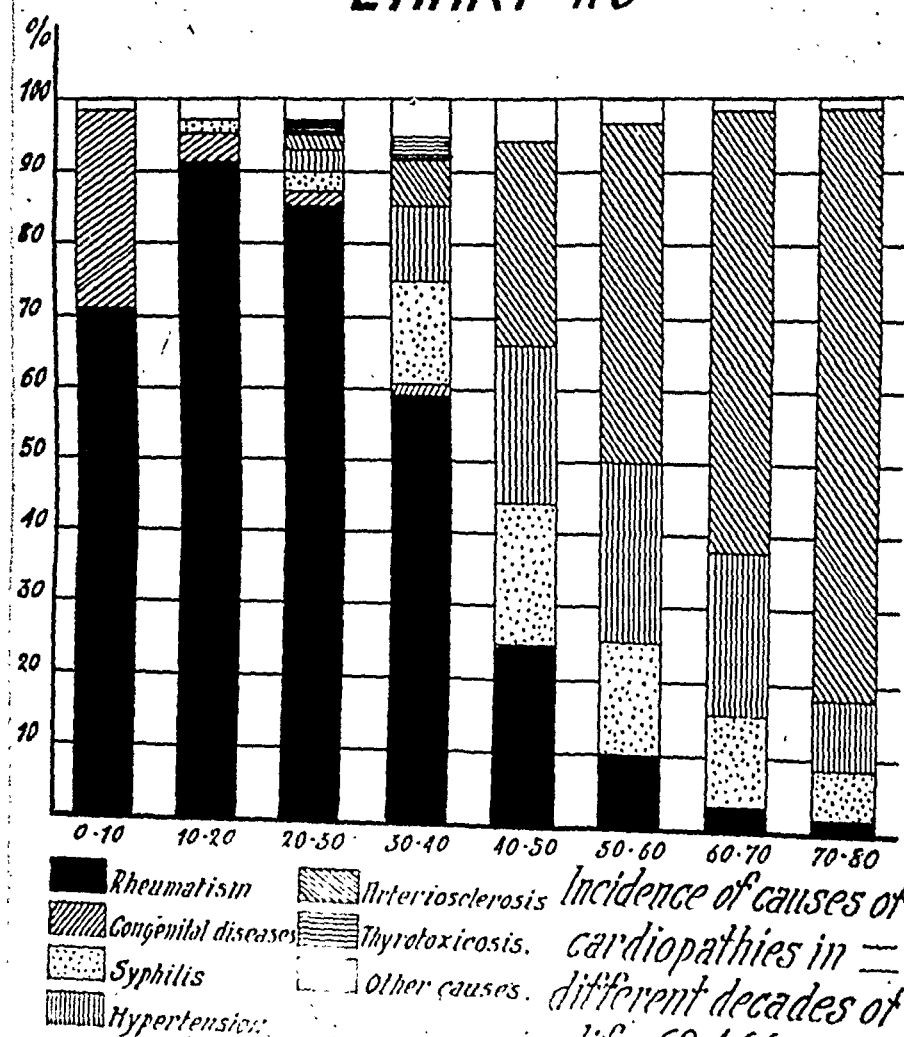
ARTERIOSCLEROSIS

Chart 5 shows the incidence of arteriosclerosis, with and without hypertension. The mean is similar to that in other countries. It should be noted that the incidence among the private patients was almost twice that in the hospital group. The males predominate, 3 or 4 to 1. Fifty per cent of the arteriosclerotic patients also had hypertension, and the proportion was higher among the private patients (56 per cent) than in

the hospital group (26.5 per cent). The incidence of arteriosclerosis among our Indians is not much lower than in other countries, and that is why the extreme infrequency of hypertension, angina pectoris, and coronary thrombosis is so striking.

Chart 6 summarizes the incidence of the various kinds of heart disease in the different decades of life. In the first two decades, rheumatic and congenital heart disease predominates, whereas, after the age of 60, arteriosclerosis and hypertension preponderate.

CHART #6



SUMMARY AND CONCLUSIONS

1. A series of 2,400 cases of heart disease was analyzed. Seven hundred twenty-six of the patients were taken from the cardiological service of the General Hospital, and were seen during the last ten years. The remainder, numbering 1,674, were private patients whom I examined in

the last five years. Leaving out disturbances of nervous origin, Table II gives the incidence of the various kinds of heart disease.

TABLE II

	NO. OF CASES	PER CENT
Rheumatic heart disease	986	41.0
Bacterial endocarditis	9	0.4
Cardio-aortic syphilis	270	11.2
Hypertension	328	13.6
Arteriosclerosis	679	28.3
Congenital heart disease	43	1.8
Thyrotoxicosis	35	1.4
Miscellaneous (cor pulmonale, anemia, cause not ascertained)	50	2.0
Total	2,400	99.7

2. The fact is emphasized that in Mexico, with its diversified, but predominantly semitropical, climate, rheumatic heart disease is as prevalent as it is in England and the northern part of the United States. Attention is also called to the enormous incidence (61.9 per cent) of rheumatic heart disease in the poor and the Indian population (either pure or with a little admixture). This figure is probably not exceeded in any other country.

3. Pure hypertension is very rare among the poor and Indian population. The incidence was 2.6 per cent, and rose to only 7.3 per cent when the arteriosclerotic cases with hypertension were added, whereas, among the private patients, who were pure white, or "mestizos" with a little Indian blood, the incidence was 36.9 per cent. It is suggested that the slow and unharassed life which the Mexican Indian has lived for centuries explains this disproportion.

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DISCUSSION

DR. GEORGE HERRMANN, Galveston, Texas.—We are certainly most deeply indebted to Professor Chávez for making the long trip to bring to us these striking original statistics. Those of us who have visited Dr. Chávez in Mexico have enjoyed his gracious hospitality and have been impressed by his demonstrations and observations.

I have made many holiday trips to Mexico to learn the "mañana attitude" as a preventative for hypertensive disease, and also to learn from Professor Chávez the story of rheumatic carditis in Mexico. This prompted our comparative study, recently interrupted by illness but partially presented at Boston, of the matter of rheumatic carditis in various localities in the South.

From autopsy studies we learned of the relatively high incidence of rheumatic carditis at Atlanta (3 per cent, Claybourne and Wolfe). In New Orleans, between 1920 and 1930, the figures were about the same, about 3 per cent, but in the last decade the autopsy incidence has dropped to about 1.5 per cent, according to Baker and Houlebek. In Galveston, the percentage was found to be 0.8 per cent. Traveling further west, to the El Paso area, and the plateau in west Texas, which is an extension northward of the Mexican plateau, we find a definite increase again in rheumatic carditis. This reaches through the Texas panhandle into the Rocky Mountain region, where there is much rheumatic carditis which Dr. Burnett could tell us more about. The altitude, I believe, must be a factor in that.

We have noted in our series that about 50 per cent of the patients have come from outside Galveston, Texas, and the Southwest, and second, that the average age at death of our rheumatic cardiacs is considerably higher than elsewhere.

Is the rheumatic patient, after he comes to the Southwest, doing better? Apparently he lives longer. Is there not a possibility that the disease often heals completely in the Southwest?

I do not think that we can emphasize too much the significance of the studies that Dr. Chávez is making. His Institute of Cardiology is certainly the broadest in its scope in the hemisphere, and probably in the world. It is an ideal concept which we should emulate. It will probably continue to furnish us with important data on the etiology, epidemiology, social side, and many other phases of cardiovascular disease.

DR. T. DUCKETT JONES, Boston.—With Dr. Herrmann, I would like to add my congratulations and thanks to Dr. Chávez for coming so far to give us this interesting information. The data seem more pertinent to rheumatic fever and rheumatic heart disease than to any other phase of cardiovascular disease.

It is a paradox, as pointed out by Dr. Herrmann, that, as one proceeds south of an area where the incidence of rheumatic heart disease is low, one finds this very high incidence reported by Dr. Chávez. Many little understood, possible explanatory features come to mind, such as climate in general, latitude, altitude, and the influence of the clinical patterns of hemolytic streptococcus infection. Regardless of what ideas one has concerning the etiology of rheumatic fever, there seems but little doubt that, from a public health point of view, rheumatic fever follows very closely the epidemiology of hemolytic streptococcus infections.

We are rapidly having to change our ideas concerning the epidemiology of rheumatic fever. For instance, Dr. Paul has reported the highest known incidence of rheumatic heart disease among the Indian school children of Montana and Wyoming. Previous ideas that there was a high incidence only in damp areas or at low altitude are hence untenable. This report helps stress the need of more extensive and comparable epidemiological studies.

I should like to ask Dr. Chávez what the general picture of hemolytic streptococcus infection is in Mexico City. Are there many cases of scarlet fever, otitis media, tonsillitis, and pharyngitis? These considerations seem very vital to the problem.

Dr. Chávez's report of this high incidence of rheumatic heart disease in Mexico City indicates that there must be an even higher incidence of rheumatic fever.

PROFESSOR IGNACIO CHÁVEZ, Mexico City, Mexico.—I said in my paper that I reserve for another study an analysis of the data on rheumatic heart disease, hypertension, and so forth. I presented here only the statistics. That is the reason I did not treat some of the points touched on by Dr. Herrmann and Dr. Jones.

It is true that, as Dr. Herrmann says, there is a good reason for the high incidence of rheumatic heart disease in Mexico City. The altitude is very high, about 7,000 feet. The climate is not tropical. We enjoy a very pleasant winter and summer. In fact, we can say that there is no winter or summer.

In the General Hospital at Mexico City there are people from all parts of the country, not only from Mexico City. Here in Cleveland you have a preponderance of patients from Ohio, and, in Boston, I think you have patients from the New England states. But in Mexico City it is different. There we have patients from all parts of the country. Of course they are more numerous from the states that are near Mexico City, but it is a coincidence that these states are almost all in the high plateau. It is the same altitude and the same kind of climate, and that is the great cause, I think, of this tremendous incidence of rheumatic heart disease.

Also, among our poor classes the incidence of infections of the throat is very, very high. We were astonished when we studied the frequency of chronic tonsillitis at autopsy. Professor Costero, one of the pathologists from Spain who is working with us in the cardiologic studies, told me that he was surprised to see the enormous number of chronic infections of the throat in the hospital patients, as compared with the incidence in Europe.

Perhaps that is a real factor in this tremendous incidence. Between 80 and 90 per cent have chronic infections of the tonsils at autopsy.

There is a third reason. As I have said, the Indians do not have hypertension, and there is not a high incidence of arteriosclerosis among them. All the rest in the statistics is for rheumatic heart disease and syphilis.

I shall try to give more details in an analytical study of each of these four larger groups later.

THE SIZE OF THE HEART AS A GUIDE TO THE TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE

THOMAS H. MCGAVACK, M.D.
NEW YORK, N. Y.

AN INCREASE in the size of the small heart characteristic of untreated Addison's disease has been observed following adequate hormonal therapy.¹ This change is reflected in teleroentgenograms which show a rising cardiothoracic ratio (C. T. R.), an enlarging frontal cardiac area (F. C. A.), and an expanding heart volume per square meter of body surface (H. V./M² B. S.). In the absence of satisfactory criteria for determining the maximum safe therapeutic dose of desoxycorticosterone acetate, cardiac size has been studied in relation to the condition of the patient while under treatment with the drug. As a result of these studies, it seems possible to formulate a definite plan of management in which the changing size of the heart acts as an indicator for the amount of sodium and desoxycorticosterone acetate to be employed in the individual patient at any given time.

METHODS AND RESULTS

The study is based upon the observation of eleven patients with Addison's disease, of whom seven have been treated with desoxycorticosterone acetate* for periods varying from ten weeks to two and one-half years.

The cardiothoracic ratio, frontal cardiac area, cardiac volume, surface area, serum sodium, and serum potassium were estimated by methods previously described.¹ Comeau and White^{2, 3} have called attention to the many potential factors of error present in any mensuration of the heart in vivo. Time of day, position, and relationship of food ingestion are important. In serial teleroentgenography of the heart, several points cannot be overemphasized: (1) Tube distance must be accurately measured. (2) The tube must be accurately and consistently centered over the same spot whenever examinations are repeated. (3) The same phase of respiration must be used in the taking of all pictures (the very end of a deep inspiration). The last factor is the one most often not fully

From the Department of Medicine, New York Medical College, and Medical Services of Flower and Fifth Avenue Hospitals, and Metropolitan Hospital, New York City.

Read before a clinical session of the Fourteenth Graduate Fortnight of the New York Academy of Medicine, Oct. 14, 1941.

Received for publication Dec. 7, 1941.

*Desoxycorticosterone acetate in oily suspension for injection and sterile compressed tablets for subcutaneous implantation were furnished by Dr. Max Gilbert, of the Schering Corporation, whose courtesy is herewith gratefully acknowledged.

controlled. Measurements are useless unless it is carefully checked. The difference between expiration and inspiration is made obvious by a single example (Table I).

TABLE I

STAGE OF RESPIRATION	CARDIOTHORACIC RATIO	FRONTAL CARDIAC AREA (SQ. CM.)	HEART VOLUME PER M ² BODY SURFACE (C.C.)
Inspiration	0.46	131.8	546
Expiration	0.35	102.3	426

In order that we may be sure two films are comparable, one may be superimposed upon the other; or the number of ribs above the diaphragm shadow may be counted; or the distance from the first rib to the shadow of the diaphragm in the midclavicular line may be measured. Variations up to 1 cm. in this last measurement may be disregarded. Moreover, the changes in the size of the heart are so striking that at times larger errors of method can be ignored.

Of 107 observations of cardiac size, eleven were made during crisis or impending crisis; eighteen, during cortical insufficiency without crisis; seventy-five, during periods of stabilization under adequate therapy; and three, when signs of toxicity from overdosage with desoxycorticosterone acetate were present. The usually accepted clinical criteria for the fully stabilized patient are a sense of well-being with return of a greater part of former vigor, a *slow, steady* gain in weight, a return of appetite, and a rising or well-sustained blood pressure. Crisis or impending crisis has been recognized only in those patients in whom salt and water balance has been disturbed sufficiently to effect a reduction in blood volume.

TABLE II

RANGE OF VALUES OF CARDIAC MEASUREMENTS IN PATIENTS WITH ADDISON'S DISEASE (107 OBSERVATIONS)

STATUS OF PATIENT	NO. OF OBSERVATIONS	C.T.R.		F.C.A. (SQ. CM.)		HEART VOL./M ² BODY SURFACE (C.C.)	
		RANGE	AV.	RANGE	AV.	RANGE	AV.
Crisis or impending crisis	11	0.25-0.36*	0.328	57.6-92.0*	76.8	208.1-383.7	302.4
Insufficiency	18	0.32-0.45	0.370	79.0-100.0	88.5	277.4-466.4	367.9
Full stabilization	75	0.40-0.51	0.435	95.0-143.0	117.1	337.8-603.6	455.8
Overtreatment	3	0.51-0.58	0.546	141.0-143.0	141.7	625.1-693.0	664.5

*Except flat chests. One patient in impending crisis showed a C. T. R. of 0.42, but the horizontal depth diameter was only 7.0 cm. so that the heart volume (228 c.c.) was actually much reduced.

Results are summarized in Table II. While there is considerable overlapping of values from one adrenocortical state to the other in such a composite chart, the average figures are sharply separated. Moreover,

if the course of a single patient is followed by serial examinations, there is no confusion of values whatsoever (K. K., Table III):

TABLE III

CARDIAC MENSURATION IN VARIOUS PHASES OF ADDISON'S DISEASE (CASE K. K.)

C.T.R.	F.C.A.	HEART VOL./M ² B.S.
<i>Crisis or Impending Crisis</i>		
0.25	57.6	208.1
0.26	74.2	263.6
<i>Insufficiency</i>		
0.32	83.8	296.2
0.38	79.6	277.4
0.34	92.4	322.0
<i>Stabilization</i>		
0.42	110.6	371.9
0.39	101.8	337.8
0.41	113.0	379.7
0.42	119.0	385.3
0.40	113.8	439.0
0.50	134.8	528.0
0.43	143.4	550.0

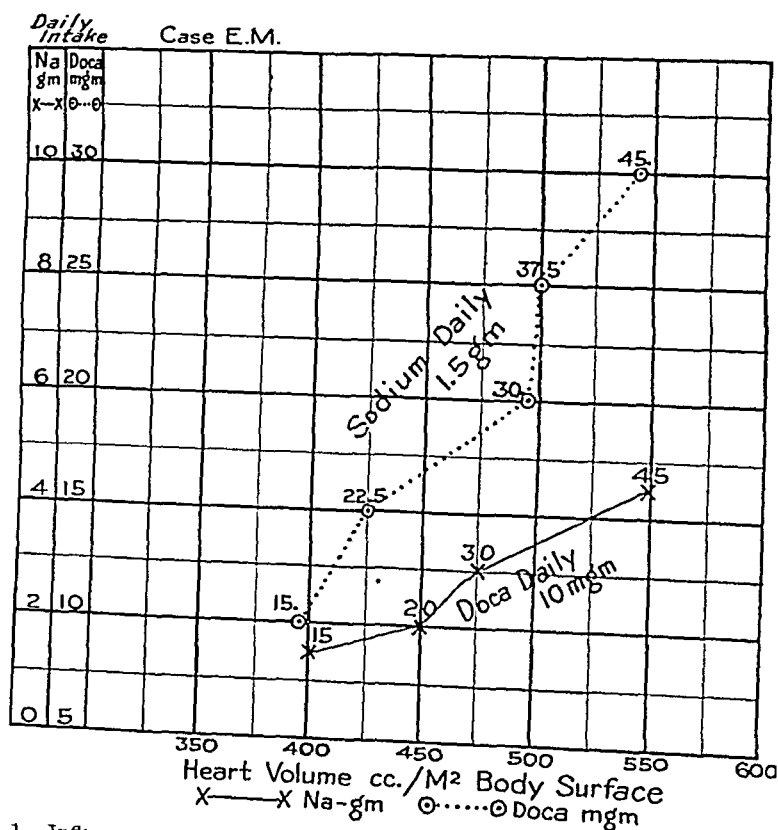


Fig. 1.—Influence of the product $Na \times D$ upon cardiac volume. (Numerals beside each calculation denote the product used for ten days or more prior to the observation.)

Two factors primarily involved in increasing the size of the heart in the patient with Addison's disease under adequate treatment with desoxycorticosterone acetate are the amount of drug itself and the amount of sodium ingested. If the daily intake of sodium is kept constant, then the size of the heart will vary directly as the amount of

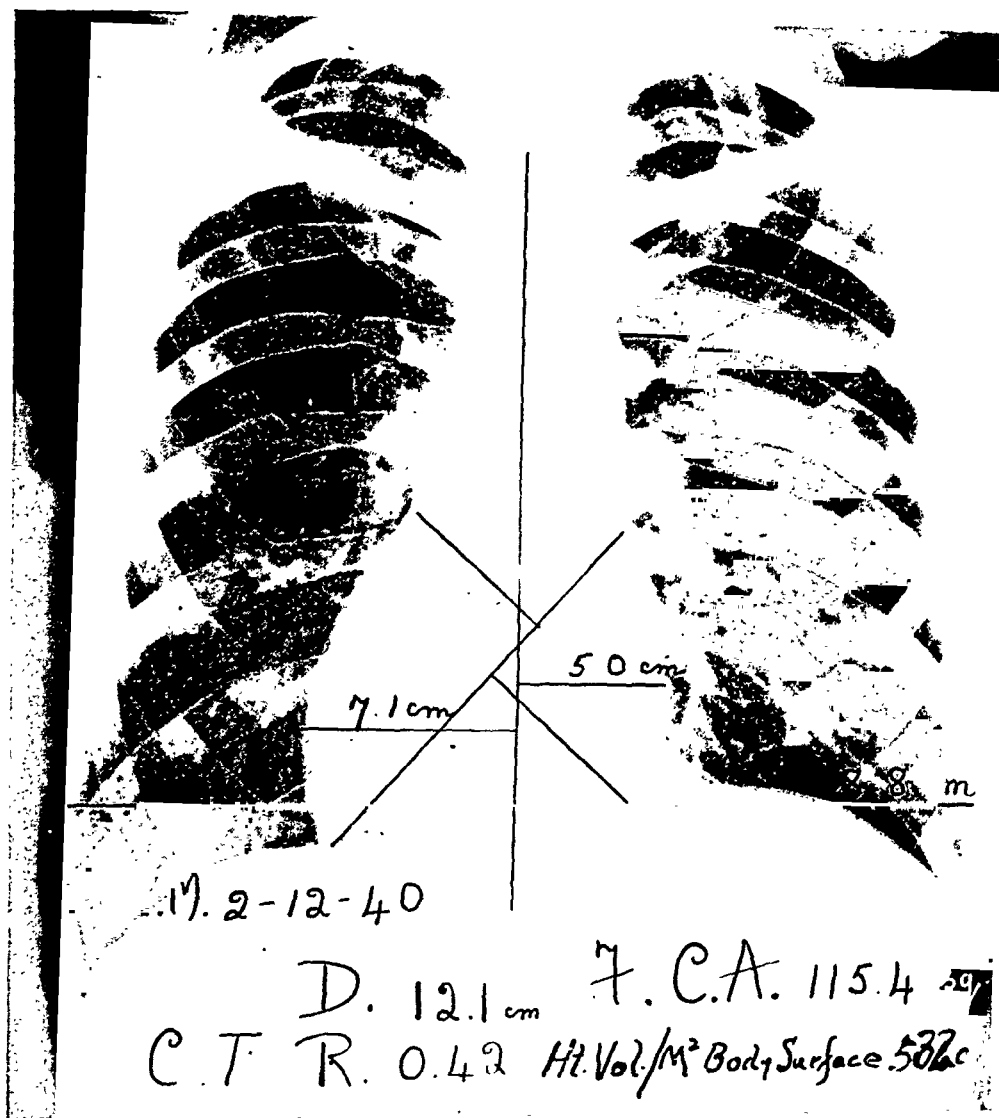


Fig. 2A.—Case E. M. The teleroentgenograms (Fig. 2A and B) illustrate the fact that either the intake of sodium or desoxycorticosterone acetate may be varied without appreciably changing the size of the heart just so long as the product of the two remains constant, according to the formula $Na \times D = K$. A. $Na = 6$ Gm.; $D = 7.5$ mg.; and $K = 45$.

desoxycorticosterone administered (Fig. 1). Conversely, if the same amount of hormone is supplied from day to day, the cardiac measurements will vary directly as the amount of sodium given (Fig. 1). The technical difficulties encountered in accurately measuring the heart have thus far made it impossible to express the above facts mathematically,

but it would appear that a straight line relationship probably exists in so far as multiple estimations in each of a series of patients are concerned (Fig. 1).

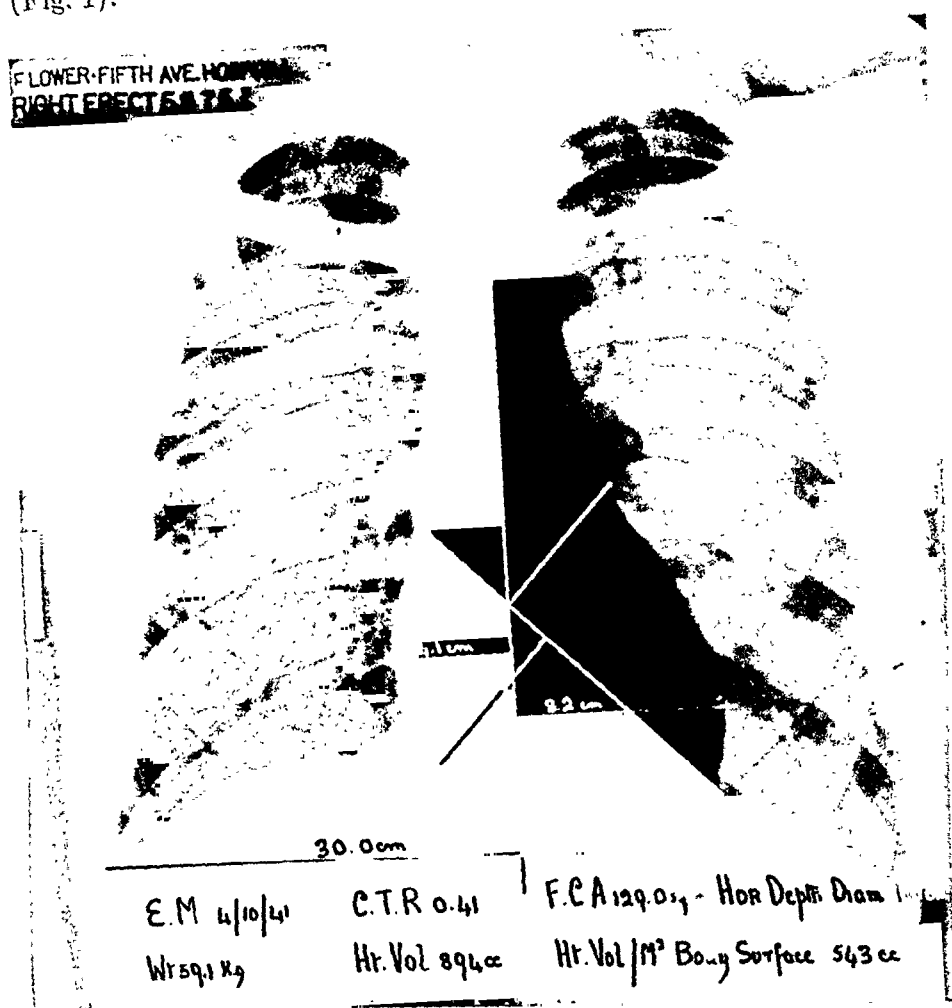


Fig. 2B.—Case E. M. Na = 1.5 Gm.; D = 30 mg.; and K = 15.

It is evident that the absolute values for either ingested sodium or desoxycorticosterone acetate, respectively, are not as important in influencing cardiac size in the treated patient as the interaction of the two in definite proportions. Ratios used in six patients and their relationship to the clinical condition of the patient have been recorded in detail elsewhere.^{4,5} Slightly different ratios are satisfactory in different patients, but in one and the same patient a nearly constant cardiac size can be maintained within limits on a constant product of sodium and desoxycorticosterone acetate according to the formula $Na \text{ (Gm.)} \times D \text{ (mg.)} = K$, where Na represents the daily intake of sodium in grams, D is the daily dose of desoxycorticosterone acetate in milligrams, and

K is a constant. Variations from patient to patient in the value for K are inevitable and depend upon the degree of functioning cortex present in the given instance.

In four patients, the sodium and desoxycorticosterone acetate have been varied in relation to each other over considerable periods of time, in such a way, however, that the value for K in the above equation for a given series of observations has remained stationary. The results are recorded in Table IV and are illustrated by roentgenograms of patient E. M. (Fig. 2A and B).

TABLE IV

RESULTS OF VARYING SODIUM AND DESOXYCORTICOSTERONE ACETATE IN RELATION TO EACH OTHER WHILE THE PRODUCT REMAINS CONSTANT

(Each ratio of Na and D was used for a minimum of three weeks)

PATIENT	Na × D	DAILY INTAKE OF		C.T.R.	F.C.A. (SQ. CM.)	HEART VOL./ M ² BODY SURFACE (C.C.)
		Na (GM.)	D (MG.)			
<i>A. In Chronic Insufficiency</i>						
K. K.	30	12.0	2.5	0.38	96.4	329
		6.0	5.0	0.39	101.8	338
		1.5	20.0	0.40	107.6	364
<i>B. In the Fully Stabilized Patient</i>						
K. K.	45	1.5	30.0	0.43	143.4	550
		3.0	15.0	0.46	129.0	530
E. M.	45	9.0	5.0	0.42	118.8	506
		6.0	7.5	0.42	115.4	532
		1.5	30.0	0.41	129.0	543
J. F.	45	9.0	5.0	0.45	112.0	506
		3.0	15.0	0.43	122.0	524
K. G.	45	6.0	7.5	0.41	101.3	442
		3.0	15.0	0.40	97.8	426

D, Desoxycorticosterone acetate; C.T.R., cardiothoracic ratio; F.C.A., frontal cardiac area.

DISCUSSION

One of the main problems in the satisfactory management of Addison's disease today is the establishment of reliable criteria by which the adequacy of treatment can be judged and by which complications may be avoided. Comment on criteria in common use will serve to show that they have too frequently been misleading, whereas the size of the heart has with one exception been informative.

1. *A Sense of Well-Being on the Part of the Patient.*—Until the use of desoxycorticosterone acetate, a sense of well-being was looked upon as one of the most useful criteria for gauging adrenocortical therapy. However, the recovery of the patient under the best of treatment is punctuated by periods in which he feels much as he did during the state of insufficiency or the impending crisis existing before therapy was started. The symptoms of such a state are also to be observed when too much desoxycorticosterone is being used.^{6, 7} The difficulty is well

illustrated by Case K. G., who was first seen in impending crisis with nausea, vomiting, anorexia, recurrent abdominal pains, faintness, and extreme weakness. The blood pressure was 85/50; serum sodium and potassium were 273.2 and 8.5 mg. per cent, respectively. The patient was given a diet containing 3 Gm. of sodium and 6 Gm. of potassium daily, and a dose of 15 mg. desoxycorticosterone acetate daily.

At the end of three weeks, during which there had been steady improvement, nausea, vomiting, faintness, and weakness recurred. The blood pressure which had been above 100 was observed at 94/62; blood serum sodium and potassium were 344.7 and 11.8 mg. per cent, respectively. It was feared that these toxic signs were due to overtreatment until roentgenograms of the heart revealed a cardiothoracic ratio of 0.37, a frontal cardiac area of 82.0, and a heart volume per square meter of body surface of 366 c.c. When these values were compared with previous films of the chest, it was obvious that these measurements indicated cortical insufficiency. Therefore, the dose of synthetic hormone was raised to 20 mg. daily, whereupon the patient began again to improve. When the patient was fully stabilized some three weeks later, a maintenance dose of 15 mg. daily was established. Had this patient not been studied roentgenographically, the drug would have been discontinued or insufficiently used, and its use looked upon as a complete failure. Under adequate dosage, she has resumed her usual life, including attention to all her duties as a housewife.

2. *Gain in Weight.*—If the gain in weight is gradual, it may usually be looked upon as an indication of improvement. At times, however, and particularly if rapid, it may be misleading, as the retention of sodium and water resulting from overtreatment with desoxycorticosterone acetate also causes upward changes in the weight. Mrs. H. L. gained 3 kg. within sixteen days, during which time the blood pressure changed from 74/44 to 132/86; serum sodium and potassium, from 305.0 and 15.6, to 373.5 and 11.6 mg. per cent, respectively; the cardiothoracic ratio, from 0.35 to 0.58; the frontal cardiac area, from 75.6 to 143.0 sq. cm.; and the heart volume per square meter of body surface, from 328 to 693 c.c. During this period the intake of sodium was 10.7 Gm. daily, and the dose of desoxycorticosterone acetate, 10 mg. Gain in weight alone would have been no index to the severe intoxication with cardiac failure which was present at the time the second group of observations was made. While such an excessive increase in weight over a short period of time would lead one to suspect the rapid retention of water, there are many instances in which the change is less obvious and even misleading, unless other criteria, including cardiac size, are carefully considered.

3. *Rising or Normal Blood Pressures.*—The blood pressure level invariably improves in the patient under adequate treatment for Addison's disease. However, its fluctuations are sometimes marked, and in our

hands it has not consistently risen into abnormally high levels when the patient was being overtreated with desoxycorticosterone acetate. The case of Mrs. H. L., cited above, is illustrative. Just prior to the development of widespread edema of the ankles and early signs of cardiac failure, this patient showed a blood pressure of 132/86, normal for her age of 53 years. Again, Mr. J. F., a 60-year-old white male was "in good clinical condition" after several weeks of treatment. The blood pressure was 100/70; weight, 36.0 kg.; serum sodium and potassium, 327.1 and 16.8 mg. per cent, respectively; the cardiothoracic ratio, 0.45; the frontal cardiac area, 105.0 sq. cm.; and the heart volume per square meter of body surface, 494.6 c.c. The sodium intake was 3.0 Gm. daily, and the dose of desoxycorticosterone acetate, 20 mg. The latter was raised to 25 mg. daily in order to carry out some studies on glucose tolerance. Eighteen days later, the blood pressure was 116/72; weight, 41.6 kg.; serum sodium and potassium, 333.4 and 14.0 Gm. per cent, respectively; the cardiothoracic ratio, 0.51; the frontal cardiac area, 112.0 sq. cm.; and the heart volume per square meter of body surface, 507 c.c. There was some evidence of increased haziness of the perihilar shadows in the teleroentgenogram of the chest. The patient stated that he "felt fine." All features of his case were normal save for the changes in size of the heart, which were abnormally high. One week later he went into acute cardiac failure with pulmonary and peripheral edema while still on the same daily intake of sodium and desoxycorticosterone. At that time the blood pressure was 148/84; weight, 41.7 kg.; serum sodium and potassium, 332.7 and 16.4 mg. per cent, respectively; the cardiothoracic ratio, 0.55; the frontal cardiac area, 141.0 sq. cm.; and the cardiac volume per square meter of body surface, 675 c.c. It is apparent that blood pressure gave no forewarning of the impending complication in this patient. Cardiac size placed us on guard more than one week before clinical symptoms of disaster were in evidence.

4. *Normal Blood Sodium Levels.*—In our hands, blood sodium levels have been totally unreliable as an index to the adequacy of treatment. Kepler⁸ expressed the same opinion. Patient K. K., observed for a little more than two years, was seen in crisis (two occasions), in cortical insufficiency, and in a fully stabilized state. The blood sodium values varied from 265 to 405 mg. per cent, but without any rational relationship to the clinical condition. On several occasions, when this patient was fully controlled, it was below 300 mg. per cent, and, at a time when he was feeling his best and all other prognostic factors were completely normal, the blood serum sodium was 284 mg. per cent. His status was satisfactory when the level was 405 mg. per cent, but he was far from as strong or subjectively comfortable as at the above period when the sodium was 284 mg. per cent.

5. *Improvement in the Blood Sugar Response to Ingested Glucose.*—With improvement in the patient's general condition, there is a return of the flat blood sugar curve to higher levels during the first three to four hours after oral ingestion of glucose. However, this relationship is not adapted to quantitative or mathematical expression.

6. *The Size of the Heart.*—This appears to be a reliable index of the clinical condition at all times.

That the size of the heart in patients with Addison's disease is profoundly influenced by the use of the synthetic hormone (desoxycorticosterone acetate) seems to be proved beyond question. Perhaps not one but a number of factors are responsible; the fundamental action of the drug is upon electrolyte metabolism. The retention of sodium with the concomitant binding of water and the stabilization of potassium equilibrium between cells and intercellular fluid appear to be of primary importance in bringing the heart back to normal size. When dosage is high enough to produce the toxic action, there is "packing" of the cells with sodium, and an increase above the normal in extracellular sodium chloride and water.* From periods of crisis through insufficiency to full therapeutic stabilization and toxic action, these effects of the hormone primarily vary inversely as the amount of sodium available within the tissues. In states of insufficiency without crisis and of full stabilization the relationship existing between the amount of sodium to be ingested and the amount of desoxycorticosterone acetate to be administered is capable of mathematical expression in terms of the previously described hyperbolic curve, $Na \times D = K$, in which values for K varying from 37.5 to 45 have been obtained in observations on seven human beings.^{4, 5, 6} We believe a liberal supply of potassium (5 to 7 Gm. daily) should be available if the above equation is to hold, although the exact amounts necessary in any given instance have not been determined.

Only a limited portion of the hyperbola just mentioned can actually be employed in the regulation of the intake of sodium and desoxycorticosterone acetate. A satisfactory range for sodium is from 2.25 to 9 Gm. daily with concomitant inverse variations in desoxycorticosterone acetate from 20 to 5 mg. daily. Such large products for sodium and desoxycorticosterone are permissible only if our criteria for determining the condition of the patient are reliable. Therefore, we believe they should be used only when cardiac mensuration is performed repeatedly and systematically. In but one of 107 observations has the heart been within normal range of size when signs of toxicity from desoxycorticosterone were in evidence. In that instance, there was a moderate elevation of blood pressure and a very slight pretibial edema, both of which disappeared spontaneously without changing the patient's regime in any way.

*There is some evidence to show that such "packing" can be prevented if liberal quantities of potassium are made available. (Ferrebee, J. W. et al.: Replacement of Potassium by Sodium in Muscles of Normal Dogs Receiving Desoxycorticosterone Acetate. [Soc. Proc.], J. Clin. Investigation 20: 445, July, 1941.)

Table IV clearly shows that the size of the heart is dependent upon the ratios of sodium and desoxycorticosterone acetate present and not upon the absolute value for the one or the other. Case E. M. (Fig. 2A and B) illustrates this perfectly. On Feb. 12, 1940, after several months of treatment with 6 Gm. of sodium and 7.5 mg. of desoxycorticosterone acetate daily the patient's cardiothoracic ratio was 0.42; the frontal cardiac area, 115.4 sq. cm.; and the heart volume per square meter of body surface, 532 c.c. On April 10, 1941, after a similar period of treatment with a daily intake of sodium of 1.5 Gm., and desoxycorticosterone acetate, 30 mg., the cardiothoracic ratio was 0.41; the frontal cardiac area, 129.0; and the heart volume per square meter body surface, 543 c.c. On both occasions, the patient was in good clinical condition, and the usual criteria of full stabilization were satisfied. However, the patient stated he felt better on the latter date when taking the larger dose of hormone, and concomitantly lessened amount of sodium. Within certain limits of dosage (up to 20 mg. daily) this patient's subjective appraisal can be made as a generalization for all of seven persons thus far observed.

Elsewhere, the dangers of high dosage with desoxycorticosterone acetate have been emphasized,¹⁰⁻¹³ and precautions in their use have been stressed.^{1, 4, 5, 9} Any one of the three heart measurements routinely employed in the present studies can be used as a reliable check to avoid overdosage. Suffice it to emphasize here the fact that, when the cardiothoracic ratio, which is extremely simple to determine, reaches or exceeds 0.50, a downward reduction in the dose of the synthetic hormone must be made if we wish to avoid a complication. The use of dosages represented on the hyperbolic curve, $Na = \frac{K}{D}$, by constants from 30 to 45, inclusive, has never produced such ratios. Therefore, such a range of values may be designated as the "zone of safe therapeutic constants."

In crisis or impending crisis, the uppermost of these constants can be safely exceeded, and here again therapy should be checked by cardiac mensuration as soon as the patient's general condition is sufficiently improved. We have used constants as high as 110 with values ranging from 11 Gm. sodium with 10 mg. desoxycorticosterone acetate to 5.5 Gm. sodium with 20 mg. desoxycorticosterone acetate). Such amounts should never be employed for more than three to four days without repeated determinations of the cardiothoracic ratio or other heart dimensions, for they have been known to cause acute cardiac failure within nine days of the time they were begun for the relief of crisis. In other words, while the usual equations for determining desoxycorticosterone and sodium intake in Addison's disease have constants which are much too low to be applied in the management of crisis or impending crisis, dosages indicated by higher figures must be discontinued as soon as the crisis is over. The condition appears to be comparable in every way to that

existing in diabetic acidosis and coma where the rules for insulin dosage in the controlled diabetic state no longer apply. The analogy may be carried one step further. There is some evidence^{14, 15} to show that in diabetes the activity of insulin varies directly as the amount of glucose available in the blood and tissues, while in Addison's disease it seems well proved that the effect of desoxycorticosterone is proportionate to the sodium present. Sodium stores are depleted in crisis; hence, the need for higher ratios of ingested sodium and desoxycorticosterone acetate is obvious.

The Cause of the Small Heart in Addison's Disease and Its Increase in Size Under Desoxycorticosterone Therapy.—Our knowledge of the pathologic physiology involved in the alterations of the size of the heart in treated and untreated Addison's disease is meager, but in connection with the observations herein detailed, several facts may warrant attention. The previous¹ and present studies make it clear that adrenal insufficiency pathognomonically decreases the size of the heart, and that a still further reduction occurs, perhaps abruptly, when crisis is superimposed upon the already existing diminished function of the adrenal cortex.

The explanation for the sharp drop in cardiac size during crisis and for the early rapid restitution under treatment seems rather simple to explain on the basis of an encroachment upon blood volume.^{1, 16} Similar downward changes in the size of the heart are seen with rapidly evolving, profuse diarrheas, excessive vomiting, severe hemorrhage, or any other condition in which there is a sudden, large drain upon body fluids. The fact that cardiac volume still remains from 15 to 20 per cent below the theoretical normal following the relief of crisis¹ while blood volume is restored to normal promptly is *prima facie* evidence that the volume of circulating blood seen in adrenal insufficiency is not alone responsible for the small heart routinely present.

Changes in water and electrolyte balance undoubtedly play a considerable role in bringing about the changes seen in the disease and in re-establishing normal conditions during treatment.¹⁷⁻²⁰ During adrenal insufficiency, water and potassium are both lost from muscle tissue, although the proportion of potassium to dried weight of the muscle remains as in the normal animal.^{21, 22} Sodium stores of the body are depleted, and the amount of potassium in the intercellular fluid and in the blood stream increases. While other changes are concomitantly present, the above alterations in electrolyte pattern are outstanding.

Whether the role of sodium, potassium, and water is a truly primary or purely secondary one in the production of the small heart of Addison's disease is as yet not entirely clear. The influence of the cortex upon carbohydrate metabolism is also a profound one. Glycogen reserves in the liver and in the heart are markedly reduced. Penn has recently cited the literature on this point.²⁴ When glycogen leaves the muscle,

potassium goes with it.^{16, 23, 24} It is difficult to say whether the status of muscle glycogen or of cell potassium is altered first. The evidence seems to favor the view that potassium is a basal factor in the syndrome of corticoadrenal insufficiency.²⁵⁻²⁹ Moreover, there is evidence to show that the action of the potassium on the heart is at least to some extent a specific effect not shared by skeletal muscles generally.³⁰

When we turn from the findings of adrenal insufficiency to the other side of the picture, that is, to the absolute and relative increase in the size of the heart in the patient under treatment for Addison's disease with desoxycorticosterone acetate, perhaps conclusions may be drawn with more certainty. Under the influence of this steroid, there is an increase in intracellular water and potassium, and a decrease in extracellular water and chloride, until such time as intoxication begins when the two latter factors increase above the original values. The handling of purely carbohydrate food is improved^{31, 32} probably through the general improvement in the state of the animal and through no direct influence upon processes fundamental to intermediary sugar metabolism.³³⁻³⁵ This improvement and a return of cell potassium to normal may combine to afford the heart a better glycogen reserve.

If the several facts cited above and assumptions based upon them are true, then the diminished size of the heart in Addison's disease is primarily a result of the loss of cellular glycogen, potassium, and water, and the restitution of size under desoxycorticosterone acetate is associated with a re-establishment of potassium and water balance with a concomitant improvement in glycogen stores.

SUMMARY

1. One hundred seven observations have been made upon the size of the heart in seven cases of Addison's disease under treatment with desoxycorticosterone acetate.

2. Cardiac size has been indicated by estimations of the cardiothoracic ratio, the frontal cardiac area, and the heart volume.

3. These measurements of cardiac size have been correlated with the clinical condition of the patient and with the intake of sodium and desoxycorticosterone.

4. The present criteria for indicating the condition of the patient with Addison's disease have been critically evaluated.

5. Rules for applying desoxycorticosterone therapy have been discussed.

CONCLUSIONS

1. In patients under treatment for Addison's disease the size of the heart increases as the clinical condition improves.

2. The first and most reliable sign of toxicity from desoxycorticosterone acetate is an abnormally large cardiac silhouette in the teleroentgenogram.

3. A reduction in the dose of hormone is advisable if the cardiothoracic ratio reaches 0.50 or above.

4. Large doses of hormone may be given with safety when cardiac mensuration is used as an objective check on the clinical condition.

5. The dose of desoxycorticosterone acetate necessary to produce a given degree of cardiac enlargement varies inversely as the amount of sodium available in the tissues.

6. The dose of desoxycorticosterone acetate should be regulated according to the formula, $\text{Na (Gm.)} \times \text{D (mg.)} = \text{k}$. Values for k of from 30 to 45 have been ascertained in a prolonged study of seven patients with Addison's disease.

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Department of Clinical Reports

COMPLETE HEART BLOCK ALTERNATING WITH NORMAL RHYTHM AND NORMAL A-V CONDUCTION

REPORT OF TWO CASES

J. MORRISON HUTCHESON, M.D., AND WELLFORD C. REED, M.D.
RICHMOND, VA.

FROM the paucity of reference to the condition in textbooks on cardiology and from the small number of cases recorded in the literature, it may be inferred that complete A-V dissociation, interrupted by periods of normal rhythm and normal conduction, is rare. For this reason the following cases are reported. Both show Adams-Stokes seizures and both illustrate the tendency, previously noted in such cases, to develop permanent block with the disappearance of attacks.

CASE REPORTS

CASE 1.—A lawyer, aged 67 years, was admitted to the Johnston Willis Hospital July 10, 1938. His chief complaint was fainting spells, which had occurred at irregular intervals and with increasing frequency for two years. The first attack occurred in July, 1936, while he was sitting engaged in conversation and lasted thirty seconds. About two months later he had a second attack and consulted a physician, who took an electrocardiogram and found no evidence of heart block, although this had been suspected. In May, 1938, attacks began to come while he was lying in bed, and one week before admission he had seven in one day. The seizures were always preceded by a feeling that the blood was leaving his head, and occasionally he seemed able to prevent them by getting down on hands and knees or by holding his head between his knees. Some attacks consisted only of faintness, while in others he became unconscious, with convulsive shaking of the body and extremities. Once, when examined during an attack, he was told that his pulse rate was 26. For a number of years he had grown progressively short of breath and had slight swelling of the ankles, but at no time had he noticed chest pain.

Physical examination showed a fairly obese man of florid complexion, 5 feet 6 inches tall and weighing 172 pounds. The pulse was regular, 40 to the minute. Blood pressure was 178/105. The heart was enlarged to the left; the aortic second sound was accentuated with a soft blowing systolic murmur at the apex. Extra sounds were heard between regular beats, and extra pulsations were seen in the neck veins. The lung bases were clear; the liver not enlarged; and only very slight pitting of the ankles was observed. Laboratory studies, including Wassermann, were essentially negative. An electrocardiogram taken a few hours later revealed normal

From the Medical Service, Johnston Willis Hospital, and the Hospital Division of the Medical College of Virginia.

Received for publication Nov. 22, 1940.

rhythm and normal conduction (Fig. 1). On the following day, although there had been no attacks, complete dissociation was present (Fig. 2). He remained in the hospital until July 31 and had a number of fainting spells and several convulsions. These were without apparent exciting cause. Efforts to obtain a tracing during an attack proved futile as the string was deflected by body movements. Atropine had no effect nor did carotid sinus pressure influence the rhythm. Ephedrine in large doses appeared to diminish the number of attacks but caused slight

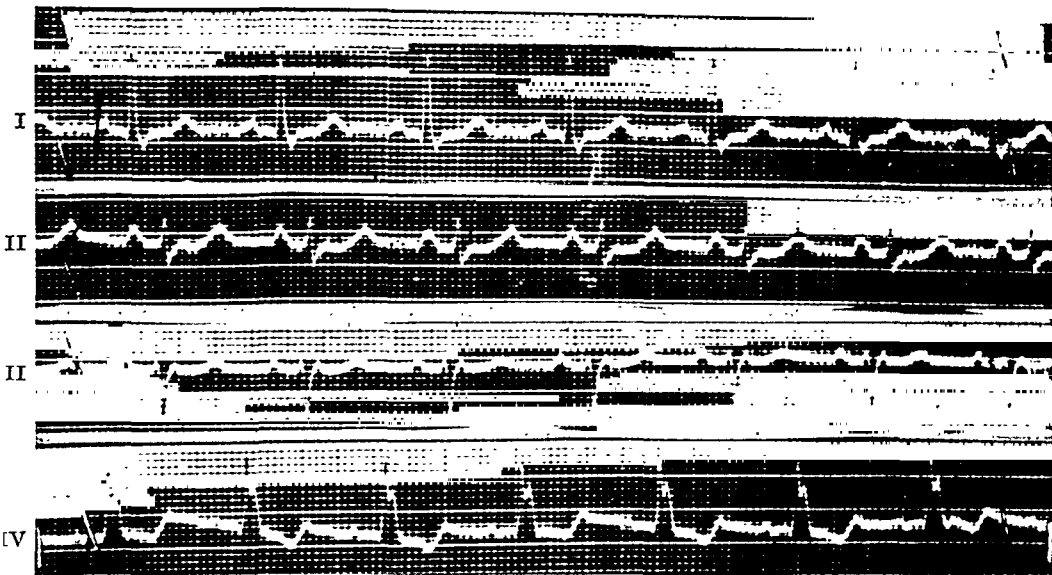


Fig. 1.—Case 1. Normal rhythm with normal A-V conduction.

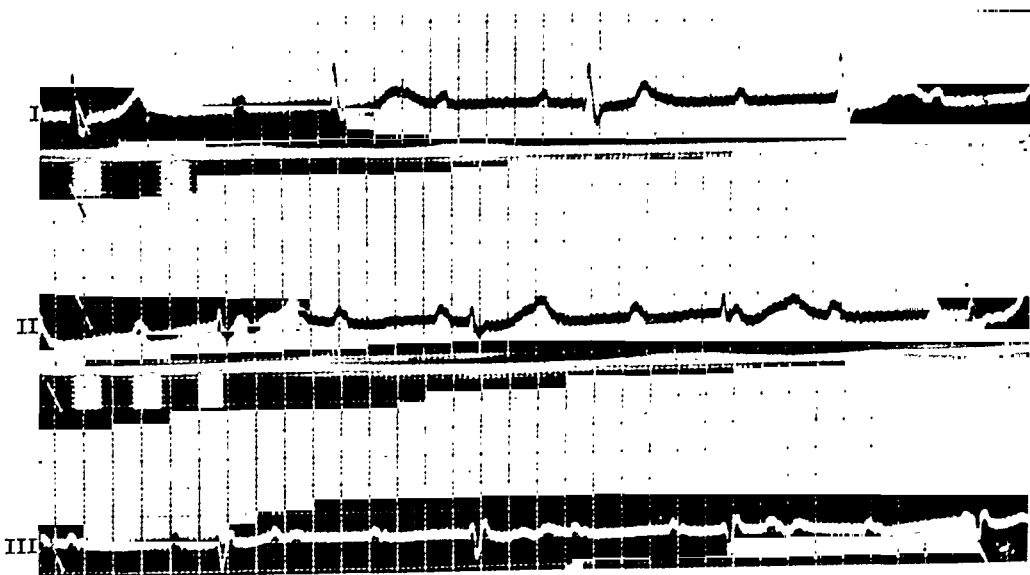


Fig. 2.—Case 1.—Complete A-V dissociation.

nervousness. On discharge he was advised to take $\frac{3}{4}$ grain ephedrine with one zanthimal tablet (theophylline and phenobarbital) every three hours when awake. This therapy was continued, and, when he was seen at the office October 3, he stated that he had had only one mild attack since August 4. At that time he showed a complete block. On December 5 he had several attacks and complete block was found. On Jan. 23, 1939, he stated that there had been no attacks in ten days.

Normal rhythm with a pulse rate of 76 was present at this time. On March 6 he reported about one mild attack a week, and on that day complete block was found. In September, 1939, attacks ceased and complete block later appeared to be persistent. Dyspnea and other evidence of congestive failure appeared, and after November, 1939, he was digitalized. On June 11, 1940, he showed evidence of mild congestive failure but was able to perform his duties as judge of a local court. Complete block was present, and digitalization had produced no measurable change in the electrocardiogram. On July 11, 1940, he died suddenly. Permission for autopsy was not secured.

CASE 2.—A married woman, aged 58 years, was admitted to the Memorial Hospital Dec. 18, 1939, complaining of high blood pressure of eight years' duration and fainting spells. Except for occasional severe headache, she had been generally well up to May, 1939, when she began to have fainting spells. These seemed to follow moderate exertion. During the spells she was unconscious for a few minutes. In two attacks she fell and struck her head. After the third attack her right arm and leg became paralyzed, but later she recovered the use of both limbs. Following this illness she was breathless after exertion and had occasional mild nocturnal dyspnea of paroxysmal character. For several months she had been having a different type of attack, which she described as "swooning." She would first notice a feeling as if her heart were turning over and almost immediately a sense of faintness, but she did not lose consciousness. The attacks bore no relation to meals or exertion.

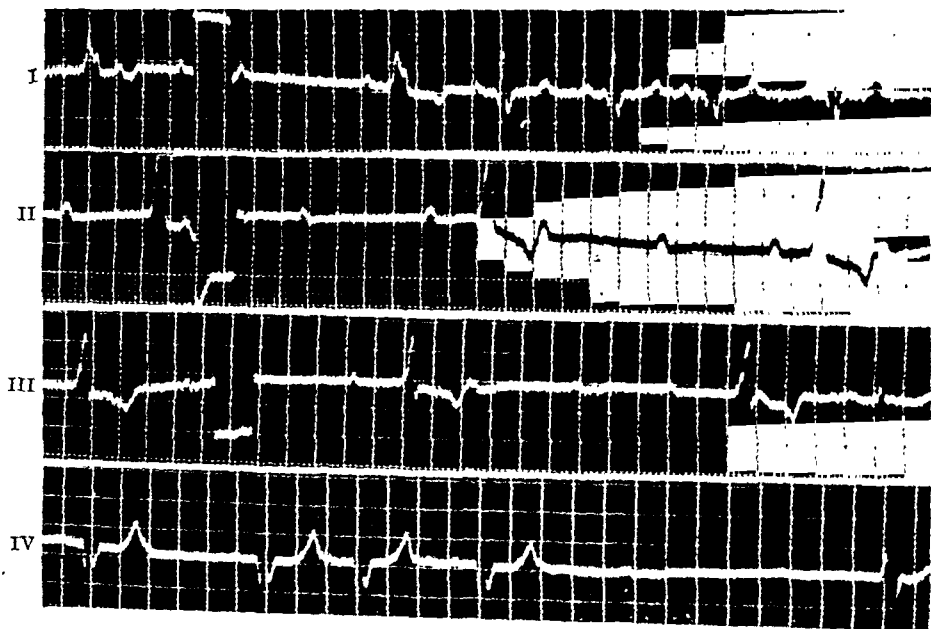


Fig. 3.—Case 2.—Complete A-V dissociation with a short period of sinus rhythm in Leads I and IV.

Examination on admission showed a regular pulse (30 per minute) and blood pressure of 180/90. The heart was markedly enlarged to the left, and a fairly loud systolic murmur was heard over the apex. A few basal râles were noted, and there was slight pitting edema of the ankles. Laboratory examinations of blood and urine showed nothing of interest. The electrocardiogram revealed complete A-V dissociation with bundle branch block and, in one record, occasional brief runs of normal rhythm and normal conduction (Fig. 3).

While in the hospital she continued to have frequent attacks. The nurse's note indicated that she would have a warning that an attack was imminent and at this time the pulse would change from the usual slow rate to 90 or above. Her face would become flushed; she would perspire profusely; and at the same time a long pause might be observed in the pulse beats, followed by a return to the slow rate. Atropine and ephedrine failed to influence the heart rate or the frequency of attacks. On December 25 the administration of benzedrine sulfate, 5 mg. three times a day, was begun and on the same day the rhythm became normal with normal A-V conduction (Fig. 4). Benzedrine was discontinued Jan. 3, 1940, but the rhythm remained normal, and there were no further attacks. She was discharged on Jan. 25, 1940. Correspondence with her physician revealed that normal rhythm persisted for two weeks after she returned home. She then began to have periods of complete block with unconscious seizures. Benzedrine sulfate was given again but was not definitely useful. Since about June 14, 1940, complete block has apparently been maintained, and there have been no attacks.

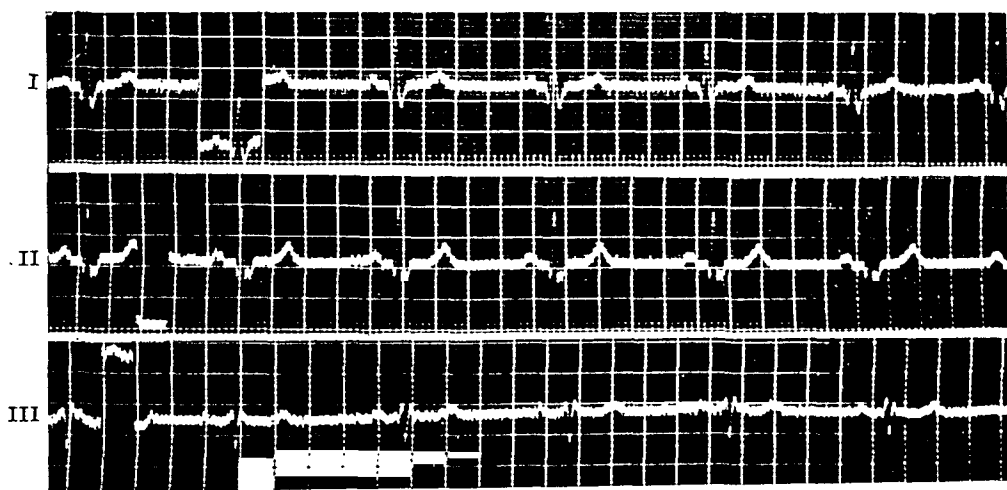


Fig. 4.—Case 2. Normal sinus rhythm.

COMMENT

Comeau¹ in 1937 was able to collect from the literature only twelve cases in which it was clearly established that a sudden transition from normal conduction to complete block with idioventricular rhythm actually occurred. To this group he added two additional cases, in one of which Adams-Stokes seizures ceased after complete block became permanent. Of particular interest in the cases here recorded are the frequent Adams-Stokes seizures, which apparently followed the shift from normal rhythm to block. In both cases the aura and in Case 2 the nurse's description of the attack and the electrocardiogram suggest that a brief run of normal rhythm occurs and the unconscious attack comes during the pause after the cessation of normal rhythm and before idioventricular rhythm begins. Both cases showed evidence of bundle branch block, which varied in degree from normal rhythm to complete block, becoming more marked in the latter. In Case 1 ephedrine in large amount seemed to diminish the number of syncopal

attacks. In Case 2 normal rhythm appeared soon after benzedrine was given and persisted for six weeks after the drug was stopped. Although it seemed unlikely that the transition was induced by the drug, the observation is of interest as Poole and Wilkinson² have reported a similar case, in which reversion to normal rhythm appeared to follow small doses of benzedrine.

Since both patients were past middle age and had hypertension and since the presence of electrocardiographic changes indicated myocardial damage, it may be concluded that the underlying pathology was cardio-sclerosis.

SUMMARY

1. Two cases showing complete A-V block with alternating periods of normal rhythm and normal conduction time are reported.

2. In both cases frequent Adams-Stokes seizures occurred during the period of fluctuating rhythm.

3. In one case definitely and in the other probably, permanent A-V dissociation was eventually established with the disappearance of syn-copal attacks.

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ANOMALOUS CORONARY ARTERIES ARISING FROM THE PULMONARY ARTERY

REPORT OF A CASE IN WHICH THE LEFT CORONARY ARTERY AROSE FROM THE PULMONARY ARTERY

LOUIS A. SOLOFF, M.D.
PHILADELPHIA, PA.

REPORTS of abnormalities of the coronary arteries in which one or both arise from the pulmonary artery are rare. A majority of the cases present a fairly characteristic clinical syndrome which should probably make antemortem diagnosis possible. Furthermore, with the increasing interest in, and growing importance of, coronary artery disease, all abnormalities of the coronary arteries are noteworthy. In these types of cases, one can learn, with almost the precision of a physiologic experiment, whether irrigation of portions of the myocardium with venous blood under low pressure is adequate to maintain its functional and anatomic integrity and, if it is not, how the heart successfully circumvents this abnormality or succumbs to it. The purpose of this paper is to report a case which presented an anomalous left coronary artery arising from the pulmonary artery with degenerative changes in the left ventricle resulting in an aneurysmal dilation of this chamber and an incidental persistence of the embryonic sinusoids and also to review the literature on anomalous coronary arteries arising from the pulmonary artery.

REPORT OF A CASE

F. P., a male infant, aged 4½ months, was admitted to the St. Joseph's hospital Oct. 13, 1940, at 7:00 P.M. and died the following morning before any studies could be made. The child was born, full term, at home, of normal parents. The infant was apparently normal at birth, but soon thereafter he began to regurgitate his food. He was brought to the pediatric clinic where the formula was changed twice with some improvement. Five days before admission to the hospital, with each feeding, the child apparently expressed severe pain by doubling up, drawing his feet up to his chest, holding himself tense and motionless and becoming cyanotic. After a few moments, he vomited his food, became pale, and perspired. Since these attacks began, the child was able to take less and less of his food without precipitating an attack. During the last two or three days, he had become visibly short of breath.

Physical examination in the hospital revealed an emaciated, slightly cyanotic, dyspneic infant with a respiratory rate of 52 a minute. There was a marked diminution of respiratory excursion on the left side anteriorly and posteriorly. No

From the Department of Medicine, Temple University Medical School.
Received for publication Nov. 29, 1940.

râles were audible. The heart sounds were normal but rapid. The provisional diagnosis was atelectasis of the left lung. The child died the following morning before x-ray or other studies could be done.

Necropsy.—Autopsy was done five hours after death. There was a moderate cyanosis of the lips, fingernails, and toenails. The anterior-posterior diameter of the chest exceeded the transverse diameter; this gave the appearance of a barrel-shaped emphysematous chest. Aside from the heart, nothing of note was found except for the adrenals and lungs. The adrenals revealed medullary hemorrhage. The lungs had several small atelectatic regions which were greatest in size and number in the left upper lobe.



Fig. 1.—Anterior view of the heart illustrating aneurysmal dilatation of the left ventricle and the huge engorged veins.

The pericardium in situ was tremendously distended. It extended 3 cm. to the right of the midsternal line and to the left mid-axillary line so that the entire left lower lobe and a portion of the left upper lobe of the lung were obscured from view. When the pericardial sac was opened, its distention was seen to be due entirely to a huge heart. The transverse diameter of the heart was 11 cm. The left lower pole of the heart was formed entirely by the left ventricle. The interventricular groove was situated 2 cm. from the left lower pole. Numerous tremendously dilated veins were present beneath the epicardium of the left ventricle. These were largest at the base of the heart where they varied in size up to 1.2 cm. in diameter, and projected above the muscular surface for as high as 1 cm. The lower half of the left ventricle bulged ventrad, to the left and cranial in an obvious aneurysmal dilatation. The ventricular muscle in this region felt extremely thin and easily compressible. The right ventricle appeared normal. The external appearance of the heart was identical with that as is frequently seen in an acute coronary thrombosis superimposed upon an aneurysmal dilatation of the left ventricle secondary to an old coronary thrombosis. The difference was the markedly dilated and engorged coronary veins. The section surfaces of the right ventricular muscle were normal. The section surfaces of the left ventricle muscle were obviously diseased. Practically no normal healthy muscle was seen. Large regions of gray fibrous tissue alternated with dull brown muscular tissue and regions of apparently acutely necrotic tissue. One

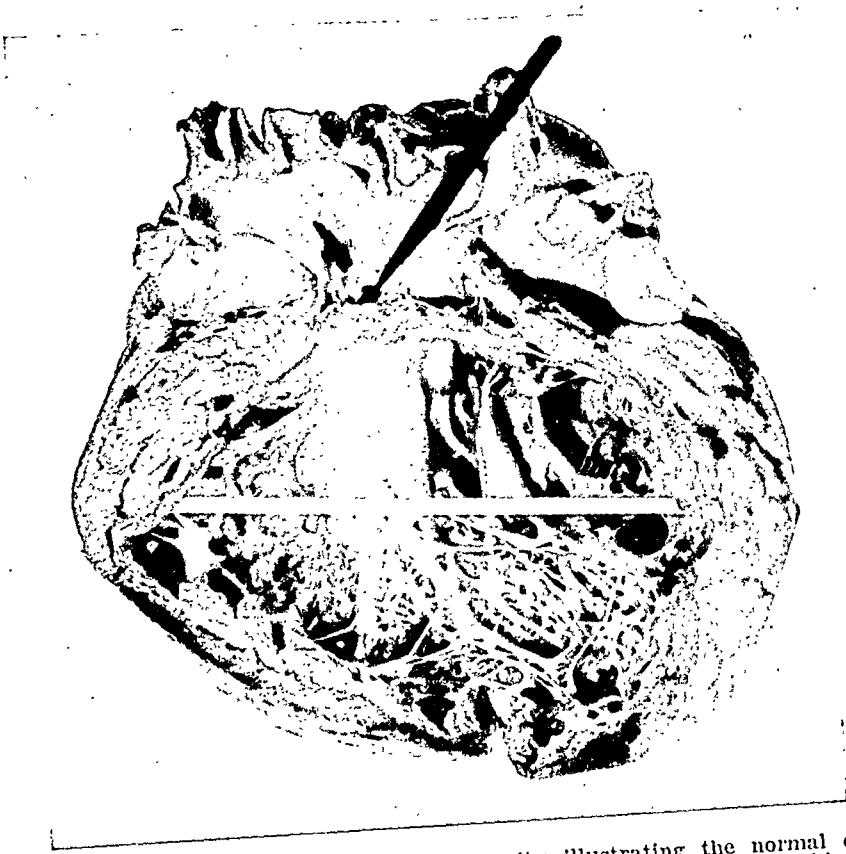


Fig. 2.—A view of the left ventricular cavity illustrating the normal origin of the right coronary artery, the necrotic muscular wall, and the hypertrophied trabeculae carneae.



Fig. 3.—The anomalous origin of the left coronary artery arising from the pulmonary artery and the comparatively small normal right ventricle.

could also see numerous large, engorged blood vessels and tiny empty spaces, the nature of which was not suspected until microscopic examination. The valves were all normal. After fixation in 10 per cent formalin, the aortic valve was 4 cm. in circumference; the pulmonary, 3 cm.; the mitral, 5 cm.; and the tricuspid, 7 cm. The right coronary artery arose at its usual site from the aorta. The ostium was approximately one-half its normal size. The left coronary artery arose from the pulmonary artery. The orifice was approximately three times that of the right coronary artery. So far as one could tell by dissection with fine scissors, the distribution of the coronary arteries was normal. The right coronary artery supplied the greater portion of the right ventricular wall and a small portion of the posterior basal portion of the left ventricle. The left coronary artery, by means of its usual two major branches, supplied virtually the entire left ventricular muscle, its finer ramifications being lost in the diseased muscle. No communications could be discovered between the major branches of the coronary arteries or between the coronary arteries and veins. The heart weighed 120 Gm. The normal for this age is approximately 30 Gm.



Fig. 4.—Left ventricular muscle illustrating necrosis, fibrosis, and calcification.

Histologic examination of the heart revealed pathology confined to the left ventricle. The right coronary artery was normal. The left coronary artery was wider than normal, but its wall was thinner than normal and thinner than the right. This was due essentially to the thinness of the media which gave the vessel the appearance of a vein except for the presence of a distinct internal elastic membrane. In the left ventricular myocardium very few coronary arterial branches

could be seen. Instead, there was an abundance of two distinct types of vessels. One type was obviously a vein. The larger ones were normal. The smaller ones were surrounded by a thick hyalinized zone of connective tissue. In many regions this zone was thicker than the entire enclosed vessel. The other type of vessel varied in size from a tiny cleftlike space to that occupying a low-power field. It was composed of a single row of flat endothelial cells. The vessels were either empty or filled with red blood cells. In some of these regions, the muscle cells were less compact than normal and resembled late embryonic heart muscle. These vessels were obviously persistent embryonic sinusoids, an interpretation which was concurred in by several outstanding pathologists to whom these sections were shown. Very little normal muscle was seen. All stages of degeneration were present. There were acute parenchymatous degeneration, hydropic degeneration, fatty degeneration, ischemic necrosis, fibrosis, and calcification.

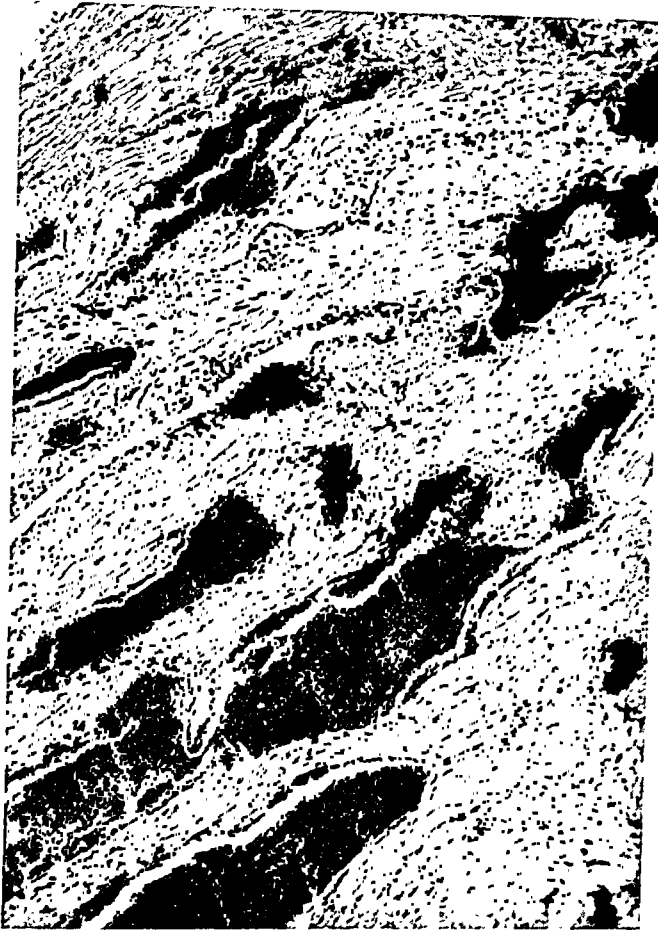


Fig. 5.—The persistence of the embryonic sinusoids.

DISCUSSION

The possibility of the origin of the coronary arteries from the pulmonary artery is due to the fact that the primitive endothelial buds which are to form the coronary arteries develop before the common arterial trunk is divided by the spiral septum into the aorta and pulmonary artery. A displacement of either the endothelial buds or the spiral septum may enclose one or both endothelial buds within the pulmonary artery. Four possibilities exist: (1) origin of the right coro-

nary artery from the pulmonary artery, (2) origin of the left coronary artery from the pulmonary artery, (3) origin of both coronary arteries from the pulmonary artery, and (4) origin of an accessory coronary artery from the pulmonary artery. The last possibility is of little importance, inasmuch as the accessory artery usually corresponds to a small branch of the coronary artery and supplies but a limited portion of the myocardium. References to this anomaly are given by Bland, White, and Garland. There have been sixteen previous reports of the left coronary artery, two of the right coronary, and two of both coronary arteries arising from the pulmonary artery. The much greater frequency of the left coronary artery arising from the pulmonary artery has been attributed to the fact that the ostium of the left coronary artery is much closer to the pulmonary sinus than is that of the left. Another believed that the greater incidence has no statistical significance because of the small number of cases.

Of the sixteen persons with an anomalous left coronary artery, eleven died in infancy between the third and fifth month and one died at the age of 10 months. The histories were all very similar. The children were born normally at term. They were apparently healthy. Soon after birth, they began having trouble with feedings.

At first there was regurgitation of food. A little later, dyspnea was present during feedings, usually accompanied by slight cyanosis. Soon thereafter, symptoms suggestive of pain occurred followed by perspiration and shock. Because all of the symptoms occurred at first only during the act of swallowing, it is very probable that these infants suffered from angina pectoris. Later symptoms of respiratory distress occurred even when the child was at rest. This gave rise to symptoms suggestive of pneumonia, which was the usual antemortem diagnosis. X-ray examination revealed a large heart. Only one case had an electrocardiogram, which showed a well-marked and late inversion of the T waves in all leads of the coronary type. The report of this last case of Bland, White, and Garland should be read for the excellent description of the paroxysmal attacks which were observed by the child's father, who was a physician. At autopsy all cases showed an enlargement of the heart, usually two to three times the normal size, with predominant enlargement of the left ventricle which had a typical aneurysmal bulge in its caudal and lateral half. Microscopically, degeneration in every way resembles the ischemic myocardial degeneration and fibrosis of coronary sclerosis except that it is more intense, more widespread, and more confluent. Heitzmann was the first to be impressed by this similarity. In order to test this similarity, a colored photograph of the heart and several microphotographic sections of the muscle were shown to several cardiologists without giving them any clinical data. The invariable diagnosis was myocardial infarction with aneurysmal dilatation of the left ventricle due to coronary thrombosis.

EMBRYONIC SINUSOIDS

The myocardium in this case differed in one respect from the heart muscle of all the other cases reported. There were numerous large and small distended and cleftlike spaces partly filled with red blood cells and lined by a single row of flat endothelial cells. These were not capillaries of the type seen proliferating in granulation tissue. They were distinctly different, as evidenced by their shape, their size, and their presence in regions where the muscle was healthy although apparently slightly embryonic. The embryonic myocardium, before the development of the coronary vessels, is nourished by blood coursing through spaces between the interlacing muscle fibers. These spaces communicate freely with the ventricular cavity. Grant, in his studies on the development of the cardiac coronary vessels in the rabbit, has shown that these spaces are reduced to capillaries by the condensation of the myocardium and persist to form an integral part of the coronary circulation. Those in the vicinity of the endocardium persist in their communications with the ventricular cavity and form the veins of Thebesius. This is the third case of persistence of the embryonic sinusoids which could be found, and it is interesting to note that the sinusoids were inadequate to prevent the degenerative changes of the myocardium.

Four of the sixteen persons lived to adulthood. Abbott's patient died accidentally at the age of 64 years. The descending branch of the left coronary artery expanded into a large triangular-shaped sinus which communicated with large thick walled vessels behind it. Rubberdt's patient was a man 27 years old who had been examined three weeks prior to his death and was pronounced healthy. He died suddenly while doing hard work. The right coronary artery was tremendously dilated and was the size of the iliac artery, 3.1 cm. in diameter. The right coronary artery anastomosed freely with the left. Kockel's patient was a man 38 years old who had had precordial pain for a few years. The heart was enlarged. There was a sclerotic patch in the bundle of His. The right coronary artery was huge. The left was larger than normal. Both coronary arteries extended to the apex of the heart. The right had apparently taken over some of the function of the left, and there were apparently anastomoses between the smaller branches of these vessels. Dietrich's patient lived to the age of 57 years. He was reputed to have been sick as a child, but adolescence was normal. Upon applying for army service, he was told that he had valvular heart disease. For ten years previous to his death he had hypertension, auricular fibrillation, and angina pectoris. Autopsy revealed aortic valvular disease and a large heart. The right coronary artery was atherosclerotic. The left, which arose from the pulmonary artery, was not atherosclerotic. There were numerous large regions of calcification. In the smaller branches of the left coronary artery and its arterioles were

invaginations of the arterial wall into the lumen which Dietrich had never seen in atherosclerosis. These findings were quite similar to those seen in the glomus tumors of the fingers; he regarded them as conclusive evidence of arteriovenous anastomoses. Injections of radiopaque substance failed to show any communication between large vessels; this was not conclusive since the heart had been previously partly dissected.

To summarize the cases of anomalous left coronary arteries arising from the pulmonary artery, the clinical history is that of an infant, apparently normal at birth, who develops usually in the third, fourth or fifth month, with the onset of active motion, difficulty in feeding, with regurgitation, dyspnea, cyanosis, pallor, sweating or shocklike countenance precipitated by the effort of eating. X-ray examination reveals a large heart. Careful fluoroscopic examination should demonstrate an aneurysmal bulge of the left ventricle. The only electrocardiogram, that of Garland et al., shows the typical coronary T wave changes which one should expect from the state of the myocardium. Life is possible if adequate anastomoses are present between the coronary arteries or between the left coronary artery and the ventricular cavity. Otherwise the retrogressive changes of tissue anoxia are too extensive to permit normal function of the left ventricle. In those cases with adequate anastomoses, symptoms may be entirely absent. Sudden death may occur. The finding of focal calcifications in the myocardium (by x-ray examination) without apparent cause in an adult should suggest this possibility. From a pathologic standpoint, it is interesting to note the differences in appearance of the left and right coronary arteries. The left coronary artery, although wider than normal, has a wall distinctly narrower than normal, due primarily to a poorly developed medial muscular coat. This suggests that the muscular coat develops in response to the increased pressure within the lumen and explains the increased thickness of this coat found so frequently in persistent hypertension. The presence of atherosclerosis in the right coronary artery and its absence in the left also point to the relation of increased work and pressure to the pathologic changes in the walls of the arteries. Such a relationship is similar to the phlebosclerosis of the inferior vena cava seen in long-continued chronic passive congestion.

Only two cases of an anomalous right coronary artery arising from the pulmonary artery have been reported. In contrast to the left, both were adults who died of unrelated disease. Monekeberg's patient was a male 30 years old who died of an epileptic fit with a fracture of the scapula and a dural hemorrhage. Schley's patient was a syphilitic man 61 years of age. In contrast to the cases with anomalous left coronary arteries, no significant pathologic changes were found in the myocardium. In these cases the right coronary artery was thin walled and

of venous character. The absence of anatomic changes in the myocardium and the absence of symptoms were attributed to adequate collateral circulation between the coronary arteries. This, however, was merely an assumption as it was not demonstrated in either case. One cannot draw a generalization on the basis of two cases. It appears unlikely that collateral circulation is more likely to occur from the left to the right coronary artery than the reverse. The explanation suggested by Linck seems more plausible. The left ventricle has more work to do and hence requires more oxygen. The oxygen content of the venous blood is adequate for the right ventricle and not for the left. It is interesting to note that, although sclerosis occurs frequently in both coronary arteries in the adult, ischemic fibrosis is rare in the right ventricle, whereas it is common in the left.

There are only two cases reported in which both coronary arteries arose from the pulmonary artery. Grayzel and Tennant's patient was a 10-day-old female with associated congenital atresia of the tricuspid orifice and interventricular septal defects. No histologic description of the myocardium is given. Limbourg's patient was also a 10-day-old infant who developed cyanosis and dyspnea after the third day. X-ray examination revealed a large heart. Autopsy disclosed tentorial tears and a large heart due predominantly to a huge left ventricle. Microscopic examination of the myocardium revealed fat droplet (hydropic?) degeneration equally present in both ventricles. Unfortunately, no illustrations of the myocardium are given. The impression obtained from reading this paper is that the histologic changes were meagre although grossly there was a disproportionate increase in size of the left ventricle.

COMMENT

From this review, it would appear that the origin of both coronary arteries from the pulmonary artery is incompatible with life beyond infancy, that the origin of the right coronary artery from the pulmonary artery is compatible with health and is asymptomatic, and that the origin of the left coronary artery from the pulmonary artery is compatible with health in the presence of an adequate collateral circulation. In the absence of an adequate collateral circulation, this anomaly gives rise to a clinical picture characterized by angina pectoris, particularly precipitated by feeding, and left ventricular failure. Anatomically (roentgenologically) a huge heart with aneurysmal dilatation of the left ventricle is found. The electrocardiogram taken in one case showed a late deep inversion of the T wave in all leads. These symptoms appear most commonly in the second or third month of life, and death usually occurs in the third to the fifth month.

SUMMARY

1. A case in which the left coronary artery arose from the pulmonary artery is described.

2. The literature of anomalous coronary arteries arising from the pulmonary artery is reviewed.

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Department of Reviews and Abstracts

Selected Abstracts

Nonidez, J. F.: Studies on the Innervation of the Heart. II. Afferent Nerve Endings in the Large Arteries and Veins. *Am. J. Anat.* 68: 151, 1941.

The composition of the aortic nerve and the distribution and structure of the aortic pressoreceptors are first considered. It is pointed out that some of the afferent fibers are very thin and give rise to terminations which lack the reticular swellings observed in the arborizations of the larger fibers (Fig. 3). These terminations, however, are regarded as pressoreceptors since they do not occur elsewhere in the aorta, left subclavian and innominate arteries. It is suggested that they are probably the last ones to cease functioning when the blood pressure reaches the 200 mm. Hg level.

The terminations in the arterial ligament are discussed in the light of the work of Takino and Watanabe, who believe that they function during fetal life. This is questioned because the physiologic activity of the pressoreceptors requires a level of blood pressure are not reached until post-natal life. It is also pointed out that some of the nerve endings in the ligament are probably terminations of parasympathetic postganglionics; this would explain the contraction of the ductus arteriosus observed by Barcroft and co-workers in guinea pig fetuses upon excitation of the left vagus.

The complexity of the receptors in the large veins increases with age. In a general way they appear more scattered than in the younger animals. The endings in the superior and inferior venae cavae persist after cervical and upper thoracic sympathectomy in the cat (Fig. 4), but the subendothelial and perimuscular endings in the pulmonary veins degenerate. This proves that the caval receptors belong to afferent fibers coursing in the vagus, but does not offer conclusive evidence as to the course followed by the fibers ending in the pulmonary veins because of the presence of vagosympathetic anastomoses.

In the pulmonary veins of puppies there are two types of afferent endings: (a) flattened arborizations located immediately under the endothelium (Fig. 5); and (b) more compact arborizations with large swellings in their branches, situated in the subendothelial layer (Fig. 6).

The role of the nerve arborizations in the pulmonary veins is taken up in connection with the researches of Daly and his co-workers on the existence of receptors in the pulmonary vascular bed. The question of the existence of receptors responsible for the pressor effects observed by McDowall and, more recently, by De Waele and Van de Velde is also considered, and it is suggested that the afferent fibers for these reflexes run in the sympathetic as well as in the vagus.

Other afferent nerve endings present in the externa of the arteries (Figs. 7 and 8) are briefly considered.

AUTHOR.

Smith, A. L.: Stethogram and Recorded Disc of Fetal Heart Sounds in a Twin Pregnancy. *Am. J. Obst. & Gynec.* 42: 908, 1941.

A stethogram of twin fetuses and the disc recording of these heart sounds, which could be audited when desired, are reported.

A twin pregnancy in which there was a question of viability of one fetus is described.

The stethogram and recorded disc of the twin fetal heart sounds made the positive diagnosis of two live fetuses, and this was confirmed by the birth of two normal babies.

This is believed to be the first stethogram and disc recording of twin fetal heart sounds reported in medical literature.

AUTHOR.

Smith, A. L.: Recording and Reproduction of a Fetal Heart Murmur Confirmed After Birth. *Arch. Pediat.* 58: 549, 1941.

It is believed this is the first report in the medical literature of a fetal heart lesion recorded in a stethogram or on a phonographic disc.

It is believed that a diagnosis of prenatal heart lesions can be made by either method.

In this case the prenatal diagnosis of a heart lesion was confirmed after birth and one year later.

AUTHOR.

Smith, A. L.: Confusion in Differentiation of Heart Murmurs and Sounds. *J. Kansas M. Soc.* 42: 457, 1941.

Murmurs may occupy any part of or be continuous throughout the cardiac cycle.

Murmurs of organic or inorganic heart origin, of intracardiac or extracardiac origin, and murmurs of all types and the various other heart sounds are often confused. This oftentimes results in unnecessary treatment or lack of necessary treatment, much to the detriment of the patient in either case.

This confusion can be prevented in most of these cases by the employment of accurate cardiac instruments.

Murmurs in themselves are no disease and need no treatment but, when accurately diagnosed, point to the underlying cause which often can be eliminated.

The earlier the recognition of the murmur and its cause, the earlier proper treatment may be instituted.

The advancement of methods of auscultation and the accurate registration of heart sound findings have increased our knowledge of the heart, but all other methods of any value must be used, as well, to arrive at a complete, accurate understanding of the condition of the heart.

AUTHOR.

Butterworth, J. S., and Poindexter, C. A.: Short P-R Interval Associated With a Prolonged QRS Complex. *Arch. Int. Med.* 69: 437, 1942.

The syndrome of short P-R interval with a prolonged QRS complex is briefly reviewed, and two cases are reported.

An experimental study of cats and dogs showed that by the use of an abnormal electrical conducting pathway it was possible to produce electrocardiographic patterns closely resembling those occurring in human beings with the syndrome.

We feel the most logical explanation of this syndrome at present is a ventricular asynchronism, with premature contraction of one ventricle activated by an abnormal conducting pathway.

Further study, with a modification of the apparatus used, may be helpful in elucidating other problems in cardiac physiology.

AUTHORS.

Geiger, A. J., Calabresi, M., and Blaney, L. F.: A Justification for the Increasing Use of Electrocardiography in Hospital Practice. *Am. J. M. Sc.* 203: 219, 1942.

The increasing use of electrocardiography in local hospital practice appears justified. Requests for routine unnecessary electrocardiograms are decried, but their liberal use, if applied judiciously and intelligently, discloses abnormalities of clinical value sufficient to warrant the extra expenditure of laboratory service.

AUTHORS.

Klainer, M. J., and Altschule, M. D.: Prolongation of the P-R Interval in Patients With Paroxysmal Auricular Fibrillation and Flutter Following Myocardial Infarction. *Am. J. M. Sc.* 203: 215, 1942.

The frequent occurrence of auricular fibrillation and flutter following cardiac infarction cannot be explained as directly due to anatomic findings, since the latter lesions are almost always ventricular.

Sixty-four per cent of patients with paroxysmal auricular fibrillation and flutter due to cardiac infarction also have a variable but abnormally prolonged P-R interval within a few days of the onset of fibrillation.

Available evidence, though scanty, suggests that the prolonged P-R interval of cardiac infarction is probably due to increased vagal activity.

Since increased vagal activity appears to be one factor responsible for the occurrence of auricular fibrillation in general, the occurrence of this arrhythmia following ventricular infarction becomes understandable.

AUTHORS.

Brody, H.: Drainage of the Pulmonary Veins Into the Right Side of the Heart. *Arch. Path.* 33: 221, 1942.

Drainage of all or of part of the lungs into the major venous system is relatively uncommon. One hundred cases, of which thirty-five represent total drainage into the right atrium or its tributaries, have been collected from the literature. Two additional cases are described; in one the pulmonary veins drained into the coronary sinus, and in the other, into the superior vena cava. Of the thirty-seven patients with complete drainage into the right side of the heart or its tributaries, only eight lived beyond six months. In all cases in which the information is available, the foramen ovale was open. In about one-half, the ductus arteriosus was closed or almost closed. In the latter, all the blood reaching the systemic circulation passed through the aortic valve and, to reach the left side of the heart, passed through the foramen ovale. As the balance between the right and the left side of the heart in these cases had to be maintained through the foramen ovale and the ductus arteriosus, the gradual closing of these, particularly the latter, might have produced imbalance, with decompensation and death. In comparing cases in which there was partial or total drainage into the right side of the heart, it appears that, when less than 50 per cent of the pulmonary return is abnormally carried into the major venous circulation, there is little likelihood of decompensation, and such persons reach adult age.

The possible embryologic explanations of these cases are briefly discussed.

AUTHOR.

Shillito, F. H., Chamberlain, F. L., and Levy, R. L.: Cardiac Infarction: The Incidence and Correlation of Various Signs, With Remarks on Prognosis. *J. A. M. A.* 118: 779, 1942.

In the fifty cases of uncomplicated cardiac infarction an analysis was made of the incidence, time of appearance, and duration of certain signs.

Increase in the sedimentation rate of the erythrocytes was observed in all but one instance. Fever occurred invariably. Other signs were less frequently present.

A rectal temperature above 104° F., a leucocyte count higher than 25,000 or a venous pressure over 200 mm. of water indicated a grave prognosis. Seven of the eight patients showing any one of these signs died within sixteen days after the coronary attack.

The level of the sedimentation rate is helpful in the differentiation between anginal pain and cardiac infarction. It is of particular value in cases of infarction with mild symptoms which are not seen by the physician during the first few days of illness. The degree of increase is not an index of the severity of the attack nor does it serve as a guide in prognosis.

AUTHORS.

Butterworth, J. S., and Poindexter, C. A.: The Formol-Gel Test in Rheumatic Fever. *Am. J. M. Sc.* 203: 278, 1942.

The formol-gel test is essentially a test for hyperglobulinemia and has no correlation with the erythrocyte sedimentation rate.

It is of little or no value in the diagnosis of acute rheumatic fever with or without carditis.

AUTHORS.

Ash, R.: Cardiac Signs in Rheumatic Infection of Childhood. *Am. J. Dis. Child.* 63: 1, 1942.

The cardiac findings in a group of 553 rheumatic children who had been observed over an average period of 9.6 years following the primary infection are described.

Thirty-eight per cent of the group presented no definite clinical evidence of heart disease during the initial illness. Signs of valvular deformity made their appearance subsequently in 19 per cent of these children, associated with acute recrudescences of rheumatic infection in 80 per cent of the cases.

There were 340 children in whom a diagnosis of heart disease had been made following onset of the infection. Regression of cardiac signs occurred in 10 per cent.

A mid-diastolic blow heard to the right of the apex in association with a systolic murmur tended to appear early in the course of acute carditis (at a time when the mitral valve is dilated rather than stenosed) and to disappear with subsidence of the infection. It would seem to be an indicator of active infection rather than a guide to the presence of a narrowed valve. An additional clue to the existence of active carditis was the presence of a high-pitched musical screech heard as a component of the systolic murmur in the region of the apex.

The diastolic thrill and rumble of the adult type of mitral stenosis had developed in somewhat less than 10 per cent of the cases, the average delay of appearance having been five years following onset of rheumatic infection.

The outcome of the disease was influenced by the type of onset, acute carditis presenting the most ominous prognosis, and chorea, the most favorable. Chorea was most common as an initial manifestation among persons who developed mitral stenosis and least common among those who developed aortic insufficiency.

Acute pericarditis was associated with the highest death rate, followed in order of severity by aortic and mitral disease and by combined mitral insufficiency with stenosis. The death rate was relatively low among those with pure mitral stenosis.

At the end of the period of observation one-fourth of the children had died of heart disease, a third of these deaths having occurred within the first year of infection. Sixty per cent of the group either had no heart disease or were not prevented by their cardiac damage from leading a normal existence.

AUTHOR.

Irving, L., Scholander, P. F., and Grinnell, S. W.: The Regulation of Arterial Blood Pressure in the Seal During Diving. *Am. J. Physiol.* 135: 557, 1942.

Although the heart of the seal slows during diving below 10 per cent of the resting frequency, electrocardiograms showed little change in individual heart beats. The pressure in the femoral artery remained at the normal level in spite of the bradycardia. An example of peripheral vasoconstriction is shown in the closure of an artery of the toe during the dive. This arterial constriction is apparently under reflex control and may be set in operation by many stimuli bearing no relation to respiration. Observed contraction of mesenteric vessels showed that there is a considerable reduction of their circulation during diving. These examples of peripheral vasoconstriction during diving along with others that are known indicate vascular adjustments which serve to maintain a normal arterial pressure which could maintain the circulation of a few tissues like the brain in spite of the extreme bradycardia.

AUTHORS.

Young, Richard H.: Association of Postural Hypotension With Sympathetic Nervous System Dysfunction; Case Report, With Review of Neurologic Features Associated With Postural Hypotension. *Ann. Int. Med.* 15: 910, 1941.

A review of the literature reveals that neurologic features are quite common in cases of postural hypotension. In recent years there has been an increasing interest in the possibility that postural hypotension is a manifestation of dysfunction of the sympathetic nervous system.

A case is reported which shows clinical features of a bradykinetic type of Parkinsonian syndrome associated with marked postural hypotension and other manifestations of sympathetic nervous system dysfunction.

As a result of pharmacologic experience in this case, it is suggested that the best method of therapy is one which produces sympathetic stimulation with ephedrine or benzedrine, and parasympathetic inhibition by drugs of the atropine group.

AUTHOR.

Luke, J. C.: The Diagnosis of Chronic Enlargement of the Leg. *Surg., Gynec. & Obst.* 7: 472, 1941.

This presentation is an attempt to organize the scattered information on the subject of the unilateral, chronic, enlarged leg so as to present a guide in its diagnosis. The subject of treatment has been excluded.

Six main groups are described, each different from the standpoint of etiology. They are: congenital hypertrophy; lymphatic stasis and obstruction, both congenital and acquired; developmental venous retardation; mixed lymphatic and venous partial obstruction; congenital arteriovenous fistulas; and miscellaneous.

Group three, that of developmental venous retardation, is presented, as far as can be discovered, for the first time and a case history is given in detail.

AUTHOR.

Antoni, Nils: Buerger's Disease, Thrombo-Angiitis Obliterans, in the Brain. Report of Three (Four) Cases. *Acta med. Scandinav.* 108: 502, 1941.

To summarize, it may be said that cerebral forms or cases of Buerger's disease are certainly not extremely rare; many patients thought to have juvenile arteriosclerosis probably suffer from this condition. One has to think of this possibility when confronted with cerebral disease in a young person, especially if the attacks are many and fleeting, and if one and the same focal sign disappears and recurs, maybe several times, perhaps to stay in the end. A combination of peripheral and central angiopathy should give special reason for suspicion. Intermittent claudication coupled with repeated cerebral insults, and perhaps cardiac disorder, should always lead to suspicions of Buerger's disease.

Unfortunately, there is not much to say about the therapy. Extirpation of the cervical ganglions and periarterial sympathectomy led to improvement in four cases from the Foerster clinic. A collection of 948 cases from the Mayo clinic in 1938 reveals, among other things, that sympathectomy does not cure the disease. If the thrombosis is primary to a certain extent, as it appears to be from the histologic picture in particular, the effects of heparin treatment should be tested. Perhaps the whole disease is a form of hypo-heparinemina.

AUTHOR.

Altschule, M. D., Linenthal, H., and Zamcheck, N.: Lung Volume and Pulmonary Dynamics in Raynaud's Disease. Effect of Exposure to Cold. *Proc. Soc. Exper. Biol. & Med.* 48: 503, 1941.

Three patients suffering from Raynaud's disease were studied as to whether their lung volume and pulmonary dynamics were abnormal and whether exposure to cold affects their pulmonary function. Abnormalities in lung volume and pulmonary dynamics were noted only in the patient with diffuse pulmonary fibrosis. Exposure to cold caused no change in lung volume or its subdivisions in any of the patients. This indicates that the blood vessels of the lungs do not react in a manner similar to those of the hand and feet. This conclusion was strengthened by the observation that exposure to cold did not result in a change in the circulation time through the lungs.

VANDELLEN.

Davies-Colley, R.: Cirroid Aneurysm. *Guy's Hosp. Rep.* 90: 134, 1941.

Six cases of cirroid aneurysm are described with the treatment.

All cirroid aneurysms are the result of a developmental defect in the formation of the capillary barrier between the arteries and the veins. The majority follow an intermediate stage of visible dilatation of the capillaries, the cavernous angioma. Trauma may play the part of an accessory factor in their formation but is never the sole cause.

AUTHOR.

Cohen, S. M.: Traumatic Arterial Spasm. *Guy's Hosp. Rep.* 90: 201, 1941.

Arterial spasm is discussed, and the literature is reviewed. Arterial spasm is shown to be a real clinical entity of special importance in time of war.

Special features discussed are the absent pulse, the duration of the spasm, pain or its absence, the use of tourniquets, and the relation of fracture and arterial damage. A number of cases are recorded to illustrate these features.

It is stressed that the use of violent traction methods may precipitate arterial spasm and that, especially in time of war with the ever lurking danger of gas-

gangrene infection, complete reduction may often be postponed for a few days with greater safety. The phenomenon of arterial spasm is critically examined, and it is recognized that much of it still requires explanation. The general features and rationale of the treatment of the jeopardized limb are discussed.

AUTHOR.

Hailey, H. R.: Popliteal Aneurysm. *Guy's Hosp. Rep.* 90: 255, 1941.

Thirty-five cases of popliteal aneurysm are reviewed. The etiology of the condition is discussed, and the importance of trauma is stressed. Syphilis does not appear to be an important cause.

The relative frequency of the symptoms and signs are analyzed. A swelling exhibiting expansile pulsation in the popliteal fossa of a young or middle-aged man of arduous occupation and intemperate habits and associated with pain in the knee or calf, and sometimes also with features of arterial occlusion forms the typical clinical picture.

The only common complication is rupture which is frequently spontaneous, and often followed by gangrene.

The various forms of treatment are detailed. Excision of the sac is advised as the method of choice in those cases in which it is technically possible.

The rarity of gangrene following operations for popliteal aneurysm is commented upon. This is apparently due to the formation of an adequate collateral circulation in most cases before operation.

In spite of this the importance of determining the efficiency of the collateral circulation before operation is emphasized. This may be done by the reflex vasodilatation test, the reactive hyperemia test, by arteriography using uroselectan, and not thorotrast which is dangerous, or by watching the effects of temporary occlusion of the main artery by a Crile's clamp.

AUTHOR.

Welch, C. E., and Faxon, H. H.: Thrombophlebitis and Pulmonary Embolism. *J. A. M. A.* 117: 1502, 1941.

It is only fair to state that the operation of ligation of the femoral vein has appealed to us more strongly as we have become more familiar with the procedure. At present, we believe that the immediate decision to be made in any given case of thrombophlebitis is whether the patient should be treated conservatively or by ligation of the vein. If conservative therapy is employed, lumbar injection of procaine hydrochloride should be done if vasospasm is considerable. If the deep venous channels are interrupted, heparin is often of value administered post-operatively. It must be emphasized that these concepts may be modified greatly as our experience increases. The important fact is that thrombophlebitis is no longer observed passively but is now accepted as a disease that must be vigorously treated.

AUTHORS.

Pelner, L., and Cohn, I. Primary Thrombosis of the Axillary and Subclavian Vein. *Am. J. M. Sc.* 203: 340, 1942.

The literature concerning primary or effort thrombosis of the axillary and subclavian veins has been reviewed. Three personally observed cases, two of which were accompanied by venography, were described. The possible causes of this condition were evaluated.

Two of our patients could not recall any injury immediately preceding the onset of the condition, but did give a history of injury some time before the thrombosis.

AUTHORS.

Fahr, G., and Ersler, I.: Studies of the Factors Concerned in Edema Formation. II. The Hydrostatic Pressure in the Capillaries During Edema Formation in Right Heart Failure. *Ann. Int. Med.* 15: 798, 1941.

The cause of edema formation in right heart failure is the rise in capillary hydrostatic pressure. Anoxemia probably plays no essential part in edema formation in right heart failure.

A tendency to edema formation develops when the hydrostatic pressure in the venous end of the capillaries rises to within 2 mm. or less of the colloid osmotic pressure. If the patient is up and about, if no precautions are taken as to salt and water restriction, and if no diuretics are given, edema will develop.

If the colloid osmotic pressure is the normal of 22 mm. Hg, edema tendency is present if the hydrostatic pressure in the venous end of the capillary is 20 mm. Hg or the venous pressure in the arm vein is 13 mm. Hg or 17 cm. H₂O.

A drop in colloid osmotic pressure of 7 mm. Hg or a rise in capillary pressure of 8 mm. Hg produces approximately the same edema tendency.

Edema tendency is present when the colloid osmotic pressure is not more than 9 mm. Hg higher than the venous pressure in the arm.

AUTHORS.

Stead, E. A., Jr., and Ebert, R. V.: Shock Syndrome Produced by Failure of the Heart. *Arch. Int. Med.* 69: 369, 1942.

A clinical picture which is similar in certain respects to that observed in surgical shock or hemorrhage is sometimes seen in patients with chronic congestive failure or with acute myocardial infarction. The patients present signs of a decreased peripheral blood flow with diminished or no radial pulse, cold extremities, narrowed pulse pressure and a relatively well-maintained diastolic pressure.

The patients with a previous history of congestive failure had an elevated systemic venous pressure. The patients with acute myocardial infarction without previous congestive failure had a normal systemic venous pressure but exhibited marked pulmonary congestion and edema.

There was evidence of slight hemoconcentration in the patients with acute myocardial infarction. This may be due to loss of fluid into the lungs.

Because of the simultaneous presence of evidence of diminished peripheral blood flow and evidence of congestion either of the pulmonary or of the systemic venous bed, it is thought that the clinical picture is produced by failure of the heart, rather than by an inadequate venous return due to a decrease in blood volume or to peripheral pooling of blood.

The terms peripheral circulatory failure and shock should not be applied to the signs of a decreased cardiac output due to heart failure. They should be restricted to those conditions in which the cardiac output is diminished because of an inadequate venous return.

AUTHORS.

Abramson, D. I., and Fierst, S. M.: Resting Peripheral Blood Flow in the Hyperthyroid State. *Arch. Int. Med.* 69: 409, 1942.

The rate of blood flow through the hand, forearm and leg was studied in a series of twelve hyperthyroid subjects by means of the venous occlusion plethysmographic method. In seven of the patients opportunity was offered to observe the changes in flow for some time after thyroidectomy.

The average resting blood flow in the forearm and leg of the hyperthyroid subjects was significantly increased over that of a control series. After thyroidectomy there was a decrease, with a return to a normal level in eleven to sixty-three days after operation.

The average resting blood flow in the hand was not strikingly increased, although some of the individual readings were significantly greater than those of the control group. After thyroidectomy in the majority of the cases the flow decreased to a subnormal level.

The rate of fall in peripheral blood flow to normal levels, subsequent to operation, occurred more slowly than did the decrease in pulse rate and pulse pressure.

AUTHORS.

Warren, M. F., and Drinker, C. K.: The Flow of Lymph From the Lungs of the Dog. *Am. J. Physiol.* 136: 207, 1942.

A method for collecting lymph from the lungs of the dog is described. The experiment requires opening the chest to expose the anterior mediastinum and artificial respiration is used during its course.

The composition of lung lymph resembles that of cardiac lymph. In eighteen dogs the average protein content was 3.66 per cent.

When artificial respiration is unduly great or when the lungs are quiescent, lymph flow is greatly reduced.

Ventilation with a mixture low in oxygen invariably increases lymph flow. If pressure in the pulmonary veins is heightened, lymph flow is greatly augmented and the lymph soon resembles blood.

The drainage of lymph from both lungs is in the main via the right lymphatic duct, comparatively little lung lymph being delivered to the circulation by the thoracic duct.

AUTHORS.

Sanches-Perez, J. M.: Cerebral Angiography. *Surgery* 10: 535, 1941.

A complete cerebral angiographic exploration can establish in many cases an exact diagnosis of a lesion which is impossible to define and to localize by other means of exploration, as in cerebral aneurysm or angioma. The author uses thorotrast and describes the technique. He states that the procedure is harmless to the patient.

NAIDE.

Gross, S. W.: Cerebral Arteriography With Diodrast, Fifty Per Cent. *Radiography* 37: 487, 1941.

The injection of 50 per cent diodrast into the common carotid artery uniformly resulted in good visualization of the cerebral circulation. The technique of administration is fully described.

NAIDE.

Clagett, A. H., Jr.: Cardiac Roentgenology: The Value of Exact Cardiac Measurements. *Am. J. Roentgenol.* 46: 794, 1941.

As a whole, the cardi thoracic ratio is unreliable as an index of cardiac abnormality. It is felt that too much stress is being placed upon cardiac measurements, especially the cardi thoracic ratio. The greatest amount of information obtainable from the roentgenologic study of the heart is the configuration of the

cardiac silhouette. This is best obtained by a careful roentgenoscopic study with visualization of the esophagus followed by an orthodiagram or a teleroentgenogram. As such, and used only as an adjunct to clinical methods, the roentgen ray can be of great value in the diagnosis of heart disease.

AUTHOR.

Brock, R. C.: Brachial Artery Embolectomy. Report of an Unusual Case. *Guy's Hosp. Rep.* 90: 230, 1941.

A case is reported in which six (possibly seven) embolisms had occurred over a period of eight years in a man suffering from auricular fibrillation and mitral stenosis.

These emboli had led to a right hemiplegia with aphasia, gangrene of the right leg necessitating amputation, and ischemic necrosis of the left anterior tibial muscles causing paralysis and deformity of the left leg. His only remaining useful limb, the left arm, was threatened by a seventh embolus which lodged in the left brachial artery. Operation was performed some seven hours after embolism, and the artery was repaired by suture after removal of the embolus. Immediate and dramatic restoration of the circulation in the limb followed. Convalescence was uneventful.

AUTHOR.

Spalding, J. E.: Periarteritis Nodosa and Its Surgical Significance. Report of a Case. *Guy's Hosp. Rep.* 90: 234, 1941.

A case of periarteritis nodosa simulating chronic cholecystitis with gallstones is described. The diagnosis was made by histologic examination of the organ. After operation, general symptoms of the disease appeared.

Although periarteritis nodosa is a nonsurgical condition, it is of interest to the surgeon because of its occasional close mimicry of acute or subacute surgical diseases, more especially of the abdomen. Sometimes a true surgical emergency may be caused by it.

The full clinical picture is outlined, in the polysymptomatic cases the correct diagnosis should be made, but when the first symptoms suggest an abdominal emergency (such as acute appendicitis, simulated by a hematoma) a correct clinical diagnosis may be impossible. In such cases histologic examination may indicate the correct diagnosis.

AUTHOR.

Woods, W. W., and Peet, M. M.: The Surgical Treatment of Hypertension. II. Comparison of Mortality Following Operation With That of the Wagener-Keith Medically Treated Control Series: a Study of Seventy-Six Cases From Five to Seven Years After Operation. *J. A. M. A.* 117: 1508, 1941.

The prognosis of patients with a high level of blood pressure and angiospastic changes of the retinal arterioles is much more favorable following operation than following medical treatment.

The surgical treatment of patients with malignant hypertension has resulted in a survival of 33 per cent after five years, whereas following medical treatment in the control series the mortality was more than 99 per cent.

In general, a favorable prognosis following operation seems to depend on a minimal degree of retinal arteriolar sclerosis rather than on the level of blood pressure, or the absence of retinitis with hemorrhages and exudates, or papilledema.

AUTHORS.

Jensen, H., Corwin, W. C., Tolksdorf, S., Casey, J. J., and Bamman, F.: Reduction of Arterial Blood Pressure of Hypertensive Rats by Administration of Renal Extracts. *J. Pharmacol. & Exper. Therap.* 73: 38, 1941.

A method is described for the preparation of renal extracts which are capable of reducing the blood pressure of rats with experimental hypertension. A total dose of 58 Gm. equivalent of fresh hog kidney, injected intramuscularly twice daily for a period of four days, was found to produce a pronounced and prolonged lowering of the blood pressure.

Oral administration of similar renal extracts at comparatively high doses failed to produce a comparable effect on the blood pressure.

Extracts of beef liver and muscle prepared according to the same procedure as employed for renal extracts failed to lower the blood pressure in hypertensive rats.

The failure of hog renin to produce a lowering of blood pressure in hypertensive rats in our routine four-day test seems to militate against the interpretation that the antipressor effect of renal extracts might be due to the formation of an anti-renin substance.

AUTHORS.

Mudd, S., and Flosdorf, E. W.: Blood and Blood Substitutes in the Treatment of Hemorrhage, Secondary Shock and Burns. *New England J. Med.* 225: 868, 1941.

The role of blood and blood substitutes in the treatment of hemorrhage, secondary shock, and burns is briefly discussed.

Human plasma and serum are the most effective agents for restoring the volume of circulating fluid to normal in cases of shock and burns, as well as of hemorrhage in the absence of excessive bleeding.

Although serum and plasma are most easily and economically preserved in the liquid form, drying from the frozen state by the lyophile, cryochem and desivac processes is recommended for war purposes and under conditions requiring prolonged storage or transportation.

AUTHORS.

Barondes, R. deR.: Night Blindness: Its Treatment With Vasodilating Drugs. *M. Rec.* 154: 427, 1941.

When the retinal arteries, arterioles and capillaries become spastic, or mildly sclerosed as a result of disturbances of innervation, etc., the vessels are unable to deliver the amount of blood to the nerve endings in the light-perceiving layer of the retina. Consequently a state of nutritional increase of visual purple arises in these parts, and the metabolic increase of visual purple cannot take place. Without ample regeneration, a depletion of this night-seeing agent results, and the reaction to faint illumination, as in darkness, becomes very poor.

The administration of vasodilating drugs markedly increased the eyes' sensitivity to faint light. The drugs which can accomplish this are nitroglycerine, thiocyanates, strychnine, hexanitrate, erythrol nitrate, and erythrol succinate. However, in advanced arteriosclerosis little vasodilatation can be expected.

AUTHOR.

Book Review

LA ENFERMEDAD REUMATICA: By Domingo Urrutia M., Jefe de Clinica Médica, and Samuel Vaisman B., Ayudante de Clinica Médica, Universidad de Chile. Imprenta "La Sud-America," Santiago de Chile, 1941, 191 pages, 22 illustrations.

This is a report which was presented at an annual meeting of the Medical Society of Santiago.

After a chapter on the social importance of rheumatic infection, the authors discuss the etiology and pathogenesis of the disease. The infectious theories are reviewed, and the allergic theory is emphasized. Predisposing causes, such as heredity, sex, climate, and focal infection, are considered. The value of tonsillectomy is underestimated in the prevention of rheumatic fever. The authors admit that the cause of the disease is still unknown, and that the observed lesions are the result of sensitization to different bacterial proteins, especially from bacteria which produce acute inflammation of the throat (among which the *Streptococcus hemolyticus* is the most important). No mention is made of the possibility that a filterable virus may be the etiologic agent, in spite of the fact that valuable evidence has recently been obtained to suggest it.

Inasmuch as the pathologic changes take place in the mesenchymal tissues, typical lesions may occur in any organ. They consist of the following, in the order given: (a) exudative-degenerative changes which terminate in necrosis of the collagenous bundles, (b) proliferative changes which lead to the formation of the specific giant-cellular granuloma (Aschoff nodule), and (c) scarring of the lesions. In the heart the characteristic location of the lesions is the posterior wall of the left ventricle and the septum. The myocardial involvement is the most important, and, according to the authors, pericardial and endocardial lesions play only a secondary role in causing heart failure and death.

Rheumatic infection is regarded as a chronic disease, with acute, recurrent attacks. The myocardial lesion is constant, especially in young people. The other manifestations (polyarthritides, chorea) are said to be important only for diagnostic purposes.

The extent and severity of the myocarditis are related to the age of the patient at the time of onset of the disease, and to the duration and number of recurrences. The intensity of the myocarditis and the tendency to recurrence are inversely proportional to the age of the patient.

Sedimentation rate, roentgenologic examination, and the electrocardiogram are discussed. The prolongation of the P-R interval and the A-V block which are so commonly encountered are attributed to edema of the bundle of His and increased excitability of the vagus.

Sodium salicylate and aminopyrine are regarded as useful in the treatment of the joint manifestations, but have no effect on the cardiac involvement. These drugs are said to be antiexudative and antiallergic.

The prophylaxis of the disease is discussed.

ALDO LUISADA.

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American Heart Journal

VOL. 24

AUGUST, 1942

No. 2

Original Communications

THE EXPERIMENTAL SIMULATION IN THE DOG OF THE CYANOSIS AND HYPERTROPHIC OSTEOARTHIROPATHY WHICH ARE ASSOCIATED WITH CONGENITAL HEART DISEASE

MILTON MENDLOWITZ, M.D., AND ALAN LESLIE, M.D.
NEW YORK, N. Y.

THE fundamental disturbance in the cyanotic form of congenital heart disease is a shunt of unaerated blood into the systemic circulation. The purpose of our experiments was to establish such a shunt and to study the resulting circulatory and skeletal changes.

Many attempts have been made to establish fistulae between vessels containing aerated and unaerated blood. For example, anastomoses have been made between systemic artery and vein¹ and systemic artery and pulmonary artery.² Fistulae have also been created between the left and right auricles or ventricles.³ It is apparent, however, that, at the sites of these anastomoses, aerated blood is at a higher pressure than unaerated blood. Since blood flow is always in the direction of lower pressure, aerated blood is introduced into the pulmonary arterial circulation, but no unaerated blood enters the systemic arterial circulation. There can consequently be no cyanosis.

Up to the present time, there has been no established method of shunting unaerated blood into the systemic circulation. In such a shunt, the pressure in the vessel carrying unaerated blood must exceed the pressure in the vessel carrying aerated blood. Such a pressure relationship is not found in the greater circulation. It does exist, however, in the lesser circulation, in which the best site for an anastomosis is at the place of contiguity of the pulmonary artery and the left auricle. After many unsuccessful trials, we were able to establish this anastomosis in four dogs.

From the Laboratories of The Mount Sinai Hospital, New York.
Received for publication Jan. 2, 1942.

PROCEDURE

Mongrel dogs, weighing from 13 to 25 kg., were used. Studies were made one or two weeks before operation, several weeks after operation, and subsequently at approximately trimonthly intervals. These studies were carried out under sodium pentobarbital anesthesia, and included measurements of oxygen consumption, cardiac output, blood volume, ether and cyanide circulation time, and arterial and venous blood pressure. Roentgenograms of the anterior extremities were made from time to time. Diodrast study of the heart by the method of Robb and Steinberg⁴ was carried out on one dog. Post-mortem examinations were made on all animals.

The operative technique, described briefly in preliminary reports,^{5,6} is now presented completely and with several modifications, as follows. After the dog is anesthetized with sodium pentobarbital, a metal cannula is passed transorally into the trachea. Escape of air around the cannula is prevented by inflating a narrow cuff at the tracheal end through a side tube in the cannula. The dog is then placed

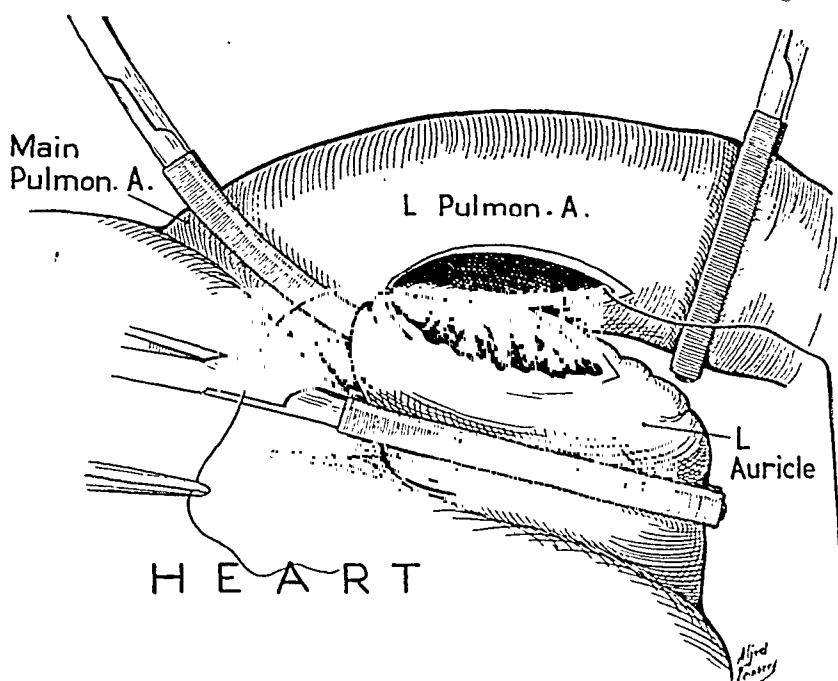


Fig. 1.—Anatomic relationships and detail of suture anastomosis.

on its right side. A sandbag is placed under the right upper anterior part of the chest. The left and right forepaws are secured above the animal's head and the hindpaws are fastened in such a way as to make the abdomen horizontal. The chest is thereby fixed in an oblique position. The incision is made in the middle of the fourth intercostal space, extending from a point 2 cm. lateral to the sternum to the edge of the long spinal muscles. Because an anticoagulant is used after operation, special care is taken to insure thorough hemostasis. After the pleura is opened, artificial respiration is carried on through the tracheal cannula by intermittent positive pressure insufflation. The ribs are then separated by a self-retaining retractor. The left lung is compressed toward the spine under wet gauze packs held in place by a retractor. An incision is then made in the pericardium, posterior and parallel to the left phrenic nerve, exposing the pulmonary artery and its left main branch, as well as the left auricle. The left pulmonary artery is dissected free, and a heavy silk ligature is passed beneath it for traction. A rubber-covered curved clamp is then applied to the main and left pulmonary artery, with its points directed toward the lung. The left pulmonary artery distal to the clamp is occluded

by the application of a short, straight, rubber-covered, intestinal clamp. If these maneuvers have been properly executed, there is now an isolated section of artery adjacent to the upper edge of the left auricular appendage. The blood flow to the left lung is completely interrupted, but the right lung receives blood which flows under the curved clamp into the right pulmonary artery. A short, straight, rubber-covered, intestinal clamp is then applied to the base of the left auricular appendage, parallel to the curved clamp on the artery, in such a way that the auricular edge is apposed to the isolated segment of artery. Parallel longitudinal incisions, approximately the length of the diameter of the left pulmonary artery, are now made in these structures. After the suture, the diameter of the anastomosis becomes about 50 to 75 per cent of the length of the incision.

Vaselinized, six-0, arterial silk, on a straight, atraumatic needle, is used for the anastomosis. An everting, running, mattress suture is used, the technique of which is illustrated in Fig. 1. Before the suture is tied, the anastomosis is filled with physiologic saline solution. The auricular clamp, distal arterial clamp, and curved clamp are removed in the order named. If the anastomosis has been successfully established, the auricular appendage is seen to balloon out during ventricular systole, and, if the auricle is palpated gently, a systolic thrill is easily felt.

The pericardium is then closed by two or three interrupted sutures, and the ribs brought together by two heavy silk sutures, each passed around the rib above and below the incision. The muscles are then approximated by running sutures, and the air in the pleural cavity is "blown off" before final closure. Artificial respiration is then stopped, and, finally, the skin incision is closed by a running suture, reinforced by one or two tension sutures. Silk is used throughout.

The postoperative administration of an anticoagulant prevents thrombosis at the fistula. In some experiments heparin⁷ was used. An initial dose of 0.4 mg. per kilogram was given, followed by the continuous intravenous administration of 0.2 mg. per kilogram per hour for three days. In other experiments, Chlorazol Fast Pink, BKS, purified by the method of Modell,⁸ was used; 0.5 c.c. per kilogram of a 5 per cent solution was administered intravenously immediately after operation, and this dose was repeated three times a day for three days. Larger doses were found to be toxic for these animals. Although heparin was less toxic, the dye was cheaper and its action more prolonged.

Certain precautions must be observed to insure success. Animals in poor condition should not be subjected to this extensive operation, which predisposes to pulmonary complications. If air is trapped in the anastomosis, there may be sudden death from air embolism, for the lungs no longer intervene between the pulmonary artery and left auricle. This is avoided by filling the anastomosis with physiologic salt solution before tying the suture. Thrombosis is avoided by careful endothelial approximation and by the administration of an anticoagulant. Hemorrhage, on the other hand, is avoided by painstaking and complete hemostasis and by careful regulation of the dosage of anticoagulant. The strictest asepsis is necessary. The dressing must be applied firmly enough for moderate local compression without compromising respiratory excursion. If postoperative pulmonary infection is suspected, sulfathiazole should be administered.

MEASUREMENTS AND CALCULATIONS

The mean arterial blood pressure was measured directly by femoral artery puncture, and the venous blood pressure, by direct puncture of the external jugular vein. The circulation time was measured with ether and cyanide, and the blood volume was ascertained by a modification of the dye method. The oxygen consumption was measured by means of a basal metabolism apparatus attached to a tracheal cannula. The oxygen content of the arterial (femoral), saturated arterial, and mixed venous

(right heart) blood was determined in duplicate by the method of Van Slyke and Neill.⁹ The right heart blood was obtained by direct puncture. The oxygen content of the saturated arterial blood was an accurate index of the blood hemoglobin. The percentage oxygen saturation of the arterial blood was calculated. The details of all these procedures have been described previously.¹⁰

Before the shunt is established, the cardiac output, according to the Fick principle,¹¹ equals

$$100 \frac{\text{oxygen consumption in c.c. per minute}}{\text{A-V difference in vol. per cent}}.$$

This represents the pulmonary volume flow in c.c. per minute, which in this case is identical with the output of the right ventricle. Since the two ventricles must expel equal quantities of blood over any period of time, the total cardiac output is twice that of the right ventricle. Communications between bronchial and pulmonary vessels and the oxygen consumed in pulmonary metabolism are not included in the calculations. These factors, however, are probably negligible.

After the shunt is established, the total cardiac output is again equal to twice the univentricular output. The left ventricular output now equals the pulmonary volume flow *plus* the volume flow through the shunt. The pulmonary volume flow, P, can be calculated from the formula,

$$P = 100 \frac{\text{oxygen consumption (in c.c. per minute)}}{\text{A-V difference (in vol. per cent)}}.$$

In the calculation of the A-V difference, the oxygen content of the mixed venous blood is determined, as before, on the sample obtained by right heart puncture. The oxygen content of the arterial blood, however, cannot be determined directly on the sample obtained by femoral artery puncture because this contains shunted unaerated blood, as well as aerated blood. To calculate the oxygen content of aerated blood, such as issues from the pulmonary veins, the oxygen content of the saturated arterial blood is multiplied by the preoperative percentage saturation of the arterial blood. This is justifiable because, with the animal breathing pure oxygen, the preoperative percentage saturation of the arterial blood varies between the narrow limits of 96 and 99 per cent, and because there is no postoperative impairment of blood aeration in the lungs. There should therefore be no significant variation in the percentage saturation of the postoperative, as compared with the preoperative, pulmonary vein (aerated) blood.

The volume flow through the shunt is calculated from a formula derived as follows:

Let x = c.c. of shunted blood in 100 c.c. of femoral arterial blood; $\therefore 100 - x$ = c.c. of aerated blood in 100 c.c. of femoral arterial blood; a = oxygen content of femoral arterial blood in vol. per cent; b = oxygen content of shunted (right heart) blood in vol. per cent; c = oxygen content of pulmonary vein (aerated) blood in vol. per cent. Then, $\frac{bx}{100}$ = c.c. oxygen in x c.c. of shunted blood; and, $\frac{c(100 - x)}{100}$ = c.c. oxygen in $100 - x$ c.c. of aerated blood. Since the oxygen content of 100 c.c. of femoral arterial blood must equal the sum of the oxygen contents of x c.c. of shunted blood and of $100 - x$ c.c. of aerated blood,

$$\frac{bx}{100} + \frac{c(100 - x)}{100} = a;$$

or,

$$x = \frac{100(a - c)}{b - c}.$$

This represents the percentage of shunted blood in the femoral arterial blood sample and $100 - x$ represents the percentage of aerated blood.

Since each 100 c.c. of blood expelled by the left ventricle contain x c.c. of shunted blood, and since the minute volume flow of blood not shunted (pulmonary volume flow), P , is known (see above), the minute volume flow through the shunt, S , may be calculated as follows:

$$S : P :: x : 100 - x;$$

$$S = \frac{Px}{100 - x}.$$

The left, and consequently the right, ventricular output, therefore, equals $S + P$.

RESULTS

Many of the experiments were unsuccessful. There was an immediate operative mortality due to accident or over-anesthesia. Many animals died because of pre-existing distemper or worms, which rendered them incapable of surviving so extensive an operation. Before proper precautions were taken, death from air embolism occurred occasionally. If the anastomosis was made too large, the consequent sudden and profound anoxemia was sometimes fatal. Postoperative pulmonary or pleural infection was not uncommon, and was probably due to the prolonged ischemia of the left lung at operation, predisposing it to infarction and subsequent infection. Pneumothorax and pleural fistula were occasional fatal complications brought about by improper closure of the chest or by wound infection. If too much anticoagulant was used or if hemostasis was inadequate, there was wound and intrathoracic hemorrhage, with or without superimposed infection. In the early experiments, when the fistula was made between the left pulmonary artery and vein, thrombosis was the rule because of angulation of the vein and because of the necessarily small size of the anastomosis. Thrombosis also occurred in the later experiments if approximation of intima to endocardium was not exact, or if too little anticoagulant was used. In one experiment, the observations demonstrated progressive narrowing and final occlusion of the anastomosis by thrombosis. Occasionally, detachment of a thrombus caused embolism in the systemic circulation. In one experiment, bacterial endocarditis was found at autopsy and was probably caused by infection of a thrombus at the anastomosis.

The results in the four successful experiments are summarized in Table I. There were no significant alterations in the arterial or venous blood pressure or in the ether circulation time. The cyanide circulation time, however, was definitely decreased in all the experiments. The percentage oxygen saturation of the arterial blood was also uniformly decreased. The greatest shunt was 47 per cent, and the smallest, 14 per cent. In the animals in which more than one postoperative study was made, there were small variations in the percentage shunt, probably because of variations in the pulmonary arterial pressure. The cell volume was increased in three of the four animals and the total blood volume was increased in the animal with the largest shunt. The hemoglobin (saturated arterial blood oxygen) rose significantly in only one dog (No. 335).

TABLE I

DOG NO.	237			262			294				335		
	2 WEEKS PREOP.	3 MONTHS POSTOP.		2 WEEKS PREOP.	1 MONTH POSTOP.	7 MONTHS POSTOP.	10 MONTHS POSTOP.	1 WEEK PREOP.	2 MONTHS POSTOP.	4 MONTHS POSTOP.	6 MONTHS POSTOP.	2 WEEKS PREOP.	3 MONTHS POSTOP.
Weight (kg.)	17.1	17.1		20.0	19.0	22.5	22.0	19.4	18.4	18.8	20.0	15.3	14.0
Arterial blood pressure (mm. Hg)	140	100		135	122	155	142	130	135	160	130	96	115
Venous pressure (cm. water)	0	1.0		2.0	3.5	2.0	4.0	2.0	2.3	2.5	2.0	0	3.0
Ether time (sec.)	4.0	3.0		2.5	3.5	3.0	2.5	2.5	3.0	-	4.0	-	-
Cyanide time (sec.)	9.0	5.0		7.0	6.0	5.5	4.5	6.5	4.0	5.0	5.0	8.0	6.0
Blood volume (c.c.)	1390	1600		2579	2254	2521	2331	2139	2031	2183	2091	1825	1786
Plasma volume (c.c.)	750	850		1625	1375	1563	1375	1250	1300	1375	1150	1150	1000
Cell volume (c.c.)	640	750		954	879	958	956	869	731	808	941	675	786
Arterial blood oxygen (vol. %)	22.15	16.51		16.57	16.39	16.68	15.48	19.11	12.90	17.0	17.21	15.92	17.54
Venous blood oxygen (vol. %)	15.57	11.62		13.92	14.05	12.75	12.65	15.88	10.19	14.02	14.33	12.99	14.32
Saturated blood oxygen (vol. %)	22.37	21.02		16.73	17.48	17.46	16.64	19.50	13.75	17.98	18.69	16.52	19.67
% saturation of arterial blood	99.0	78.3		99.0	93.7	95.5	93.0	98.0	93.8	94.5	92.1	96.5	89.2
Oxygen consumption (c.c. per min.)	117	120		144	130	153	127	113	110	127	128	108	95
Systemic blood flow (c.c. per min.)	1780	2478		5420	5537	3835	4487	3500	4057	4264	4443	3686	2951
Pulmonary blood flow (c.c. per min.)	1780	1318		5420	3987	3310	3325	3500	3343	3527	3208	3686	2039
% shunt	0	47		0	28	14	26	0	18	17	28	0	31
Autopsy findings	Died 4 months postop. Widespread pneumonia; anastomosis patent (4 mm.); pedunculated thrombus extending into auricle.			Died 11 months postop. Widespread pneumonia; anastomosis patent (4 mm.); pedunculated thrombus extending into auricle.			Sacrificed 8 months postop. Anastomosis patent and fenestrated, one opening (4 mm.) separated by thin septum from second opening (2 mm.); subperiosteal bone proliferation in long bones.				Died 4 months postop. Anastomosis patent (6 mm.); pedunculated thrombus in auricle and thrombus partially occluding left pulmonary artery distal to anastomosis; cerebral embolus.		

In the other three, it remained essentially unchanged, except for a transient postoperative anemia in one (No. 294). The systemic blood flow always exceeded the pulmonary blood flow by the volume flow through the shunt. The pulmonary blood flow was either decreased or unchanged in all four experiments. The systemic blood flow was increased in two animals and decreased in the other two. In dog No. 294 the increased systemic blood flow might have been due in part to the transient anemia. However, the cardiac output became still greater as the anemia subsided. The changes in systemic blood flow were not caused by changes in the metabolic rate, inasmuch as the oxygen consumptions remained essentially unaltered. Hypertrophic osteoarthropathy was found by roentgenologic examination (Fig. 2) in one of the two dogs with increased systemic blood flow. In none of the other animals were such bone changes found.

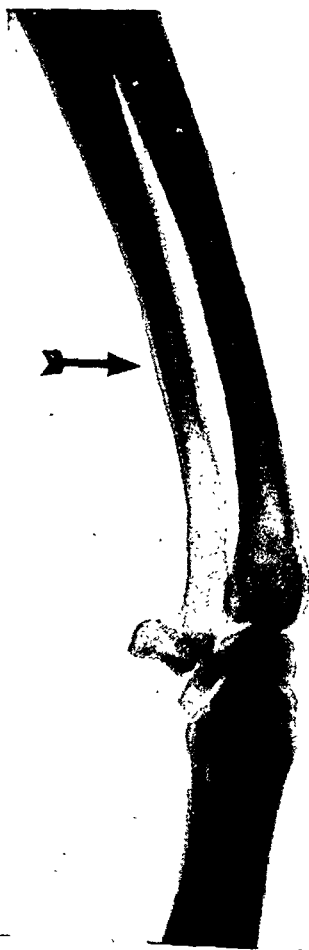


Fig. 2.—Roentgenogram of radius and ulna of dog No. 294, showing periosteal proliferation (arrow).

Isolated observations not recorded in Table I were made on several animals. Pulse rates and respiratory rates did not vary significantly. In several dogs, the heart rate and the arterial blood pressure were recorded before and after manual compression of the anastomosis at

operation. Closing the anastomosis slowed the heart and increased the blood pressure, whereas releasing the compression caused opposite changes. This effect, however, was slight, probably because of the suppression of reflexes by the anesthetic and by operative shock. A soft systolic murmur could be heard in some animals. It must be remembered that the pressure in the pulmonary artery is low, and that the intensity of a murmur would therefore be less than that of a murmur coming from the systemic circulation. Cyanosis of the tongue was observed in all the successful experiments; the degree was proportional to the size of the shunt. Increased intensity of the cyanosis after exercise or excitement was observed frequently, and was probably caused by increased pressure in the pulmonary artery, with consequent increase in the percentage shunt, and also by increased oxygen "unsaturation" of the mixed venous blood. In one animal the patency of the anastomosis was demonstrated ante mortem by the injection of diodrast.



Fig. 3.—Comparison of ulna of dog No. 294 (left) with ulna of normal dog (right).

Two of the dogs died of fulminating pneumonia four and eleven months, respectively, after operation. One animal died of a cerebral embolus, four months after operation. The source of this was a thrombus extending from the anastomosis into the auricle. The remaining dog was sacrificed eight months after operation. In all the autopsies

the anastomoses were found to be patent and their cross-section areas were proportional to the calculated percentage shunts. The largest fistula was found in the dog with the 47 per cent shunt. It admitted a lead pencil with ease. In two of the animals there was no thrombus at the site of the fistula. In the other two there were thrombi extending from the edge of the anastomosis into the auricle, and, in one of these, an additional thrombus extended from the anastomosis into the left pulmonary artery. In dog No. 294 the presence of hypertrophic osteoarthropathy was confirmed at autopsy (Figs. 3 and 4). No bone changes were found in the other dogs. Fig. 5 shows the opened main and left pulmonary artery, the orifice of the right pulmonary artery, and the patent anastomosis of dog No. 262.

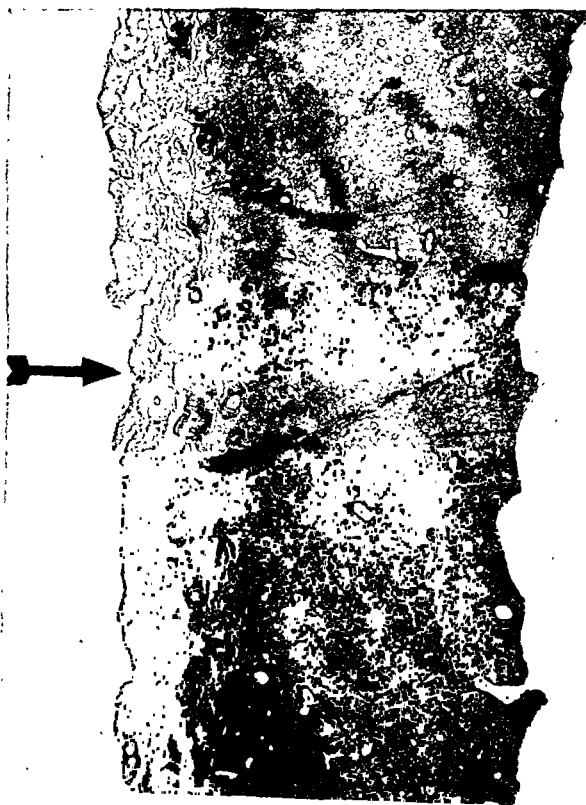


Fig. 4.—Photomicrograph of transverse section of tibia of dog No. 294, showing new-formed periosteal bone.

DISCUSSION

It is apparent from these experiments that it is possible to establish a permanent fistula between the pulmonary artery and the left auricle in dogs. Such a fistula reproduces the circulatory changes found in most cases of congenital heart disease with cyanosis,¹² as typified by the tetralogy of Fallot.

When there is an abnormal communication between vessels carrying aerated and unaerated blood, there is an increase in volume flow through

the circuit in which the pressure is lower at the site of the shunt, at the expense of the circuit in which the pressure is higher. With an arterio-venous fistula, for example, and also when the ductus arteriosus is patent, the lesser circulation not only carries all the venous return from the greater circuit, but also carries oxygenated blood shunted in from the systemic arteries. The total blood flow through the lungs is therefore greater than the total systemic blood flow. Conversely, in the cyanotic type of congenital heart disease and in our experiments, the direction of flow through the shunt is from the lesser to the greater circulation. The total systemic blood flow, therefore, exceeds the total pulmonary blood flow by the amount of blood shunted.



Fig. 5.—Heart of dog No. 262, showing opened right ventricle and pulmonary artery. RP, Right pulmonary artery orifice; LP, left pulmonary artery (opened); A, pulmonary artery orifice of anastomosis.

In addition to this relative increase in systemic blood flow, an absolute increase was also found in the two animals in which there were no obstructing thrombi. This increase in left ventricular output, as well as the increase in cell volume or total blood volume, is probably a mechanism which compensates for the chronic systemic arterial anoxemia. Because of such compensating mechanisms, the delivery of oxygen to

the tissues, in the resting state, at least, is normal despite the anoxemia, and the oxygen consumption remains unchanged. With exercise, these compensating mechanisms may break down, with ensuing tissue anoxia.

Hypertrophic osteoarthropathy has been known to occur in animals,¹³⁻¹⁶ usually in the wake of pulmonary tuberculosis or pulmonary neoplasm, spontaneous or experimental. Attempts to reproduce these bone lesions in the experimental animal have been uniformly unsuccessful.¹⁷⁻²³ In our experiments, although the anastomosis between the pulmonary artery and the left auricle was made successfully in four dogs, only one of these developed hypertrophic osteoarthropathy. It may be of importance that only in this dog was there an absolute increase in systemic cardiac output, together with a survival period long enough for bone changes to develop. The cause of the bone proliferation was not anoxia, for, despite the arterial anoxemia, the transport of oxygen to the tissues was normal because of the increased blood flow, and the oxygen consumption remained unchanged. It is possible, however, that the chronically excessive systemic blood flow increased periosteal nutrition and thus stimulated bone proliferation. Since hypertrophic osteoarthropathy occurs in human congenital heart disease with cyanosis, it is possible that a similar mechanism is responsible for the development of the bone changes.

SUMMARY

1. A procedure for anastomosis of the pulmonary artery to the left auricle in dogs is described.
2. In the successful experiments, this procedure reproduced the circulatory derangements found in the cyanotic type of congenital heart disease.
3. In one experiment, hypertrophic osteoarthropathy developed, and was apparently attributable to increased systemic blood flow.

The authors take this opportunity to thank Dr. E. Libman, Dr. G. Bachr, Dr. G. Shvartzman, and Dr. A. M. Fishberg for valuable criticism, and Dr. S. Siegal for helpful suggestions.

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THE CARDIOVASCULAR EFFECTS OF PAREDRINE

M. H. NATHANSON, M.D., H. ENGELBERG, M.D., AND J. HERSH, M.D.
LOS ANGELES, CALIF.

PAREDRINE is the name which has been given to the new epinephrinelike compound, parahydroxyphenylisopropylamine. This substance stands between epinephrine and ephedrine in chemical structure, and, judging from its chemical composition, should possess a more intense sympathomimetic action than ephedrine. The action of this compound in the prevention of cardiac standstill has already been described by one of us (M. H. N.).¹ The purpose of the present communication is to report observations on both the cardiac and pressor actions of the substance, and to discuss therapeutic applications.

CARDIAC ACTION

Although epinephrine and related compounds affect various properties of the heart, we have been chiefly concerned with the action of these drugs on cardiac standstill for the following reasons: (1) The chief therapeutic indication for the sympathomimetic amines in heart disease is in the prevention and treatment of cardiac standstill, and (2) the effectiveness of drugs on cardiac standstill can be studied in man by an accurate and well-controlled method, previously described.² This method utilizes persons who have a sensitive carotid sinus, so that prolonged cardiac arrest can be consistently and repeatedly produced by pressure on the carotid sinus. In these cases, apparently because of overactivity of the vagus nerve, carotid sinus pressure eliminates the activity of the sinus node. The cardiac standstill is caused by temporary inactivity of the sinus node and by failure of development of secondary centers of impulse initiation. The indication that a drug is effective in the prevention of cardiac standstill is the abolition of the cardiac arrest either by the restoration of the activity of the sinus node or by the development of a new impulse initiating focus. The technique of the experiments is simple. An electrocardiogram is made during the period of cardiac arrest produced by carotid sinus pressure. The drug to be tested is then administered, and the carotid sinus pressure is repeated after suitable intervals. In a previous report³ it was shown that a group of unrelated drugs, including barium chloride, calcium gluconate, digitalis, caffeine, coramine, metrazol, and thyroxine, had no

From the Department of Medicine, University of Southern California.

Read before the meeting of the American Heart Association, Cleveland, May 31, 1941.

Received for publication Jan. 5, 1942.

influence on the induced cardiac standstill. It was then demonstrated that the only effective compounds were epinephrine and chemically related substances.⁴ It was possible to ascertain the relative activities of various sympathomimetic amines by this method. In most instances the cardiac standstill was abolished by the development of a new pacemaker, usually in the ventricles. The reaction to varying doses of epinephrine was first ascertained, and it was found that the rate of impulse formation in the new pacemaker was proportional to the dose of the drug. The action of other sympathomimetic amines was then compared with that of epinephrine, and a ratio of activity was established. For example, the intravenous injection of 2 mg. of neosynephrine reproduced the effect of $\frac{1}{50}$ mg. of epinephrine, giving a ratio of activity of neosynephrine to epinephrine of 1 to 100. A number of sympathomimetic amines were studied by this method, and the comparative activity on cardiac standstill of the more important is given in Table I.

TABLE I

DRUG	APPROXIMATE RATIO OF ACTIVITY TO EPINEPHRINE
Cobefrine	1:10
Epinine	1:40
Adrenalone	1:40
Neosynephrin	1:100
Synephrin	1:400
Tyramine	1:1,200
Ephedrine	1:1,500

It was found that ephedrine was the only compound which was effective on induced cardiac standstill when given orally. However, large doses were necessary, and frequently the standstill was prevented only by amounts of the drug which produced unpleasant side effects. The observations of Alles⁵ and Alles and Prinzmetal⁶ indicated that paredrine was a stable sympathomimetic amine with greater activity than ephedrine. The effect of this drug has now been studied in sixteen cases in which cardiac standstill could be induced by pressure on the carotid sinus. The effective dose of the drug was 60 mg. in fourteen cases and 40 mg. in four, and in each instance the induced cardiac standstill was modified. The mechanism of the abolition of the standstill varied. In nine instances the standstill was abolished by the development of a rhythm which arose in or near the auriculoventricular node; in three, lower ventricular foci became active; in three instances the activity of the sinus node was restored; and in one case the rhythm consisted of sinus beats alternating with beats which arose from an ectopic ventricular focus. In five cases the activity of paredrine and ephedrine was compared, and paredrine was found to be between two and three times as effective as ephedrine. Four patients with spontaneous attacks of dizziness or syncope, associated with sensitivity of the carotid sinus,

have now been observed for periods of one year or more, and the attacks have been reduced in frequency, or eliminated, by doses varying from 40 mg. to 60 mg. three times a day (Fig. 1). The effect of the drug was also studied in six cases of heart block. In two of four cases of

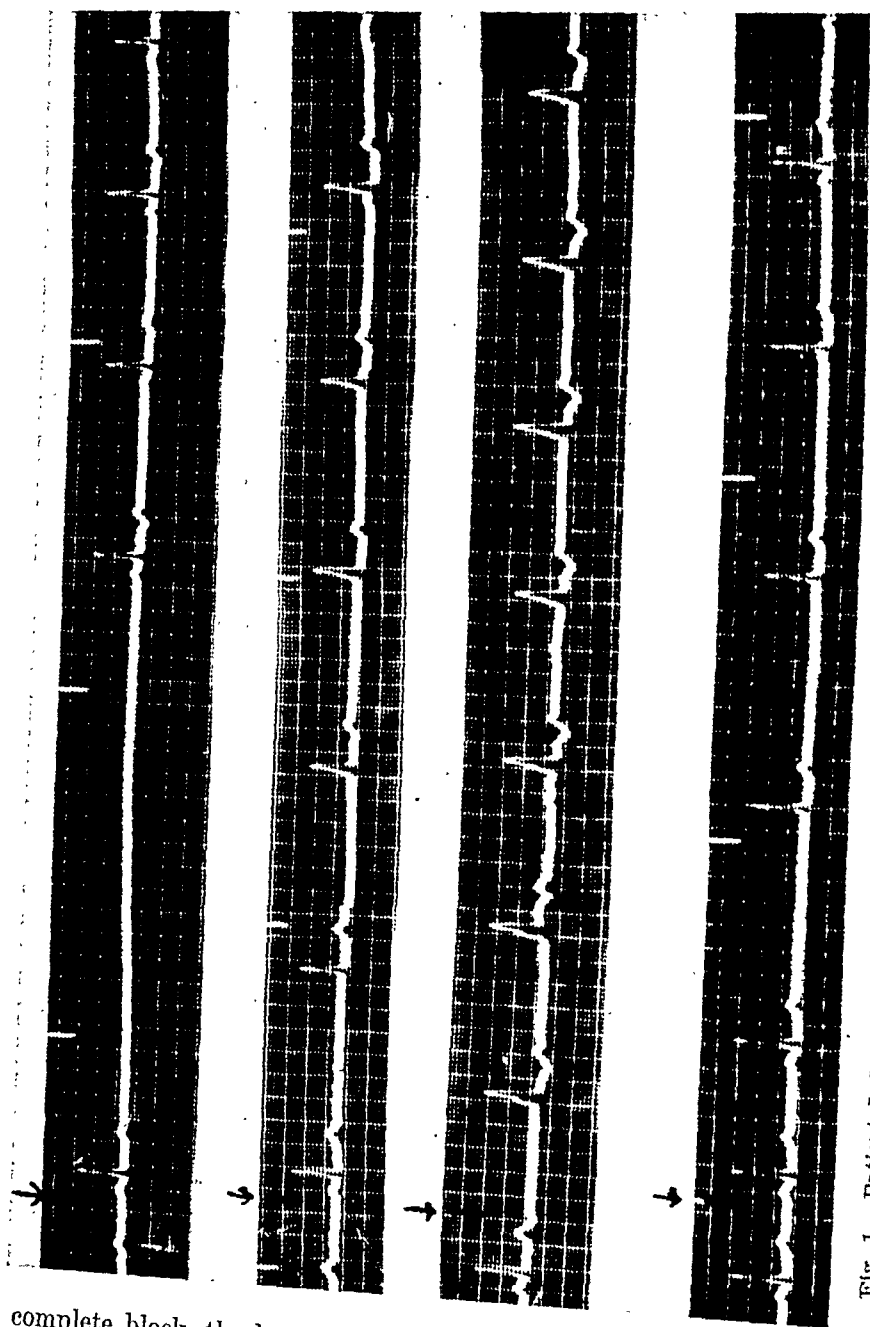


Fig. 1.—Patient I. K. History of frequent syncopal attacks which could be reproduced by pressure on the right carotid sinus. Upper strip shows standstill of five seconds induced by pressure on the carotid sinus (arrow). Lower strips show the effect of carotid sinus pressure thirty, sixty, and ninety minutes after the oral administration of 60 mg. of paredrine hydrobromide.

complete block, the latter was changed to partial block after 60 mg. of the drug. In two cases of complete block the ventricular rate was increased. In one instance of partial block (3 to 1), the block disappeared after the administration of 60 mg. three times a day for a week. In the other case of partial block the ventricular rate increased. Four patients

with chronic heart block have been followed for two years. Although they may be free of syncopal attacks for varying periods without therapy, these patients find it necessary to resume the use of the drug periodically to prevent the recurrence of attacks.

An additional advantage of paredrine over ephedrine is the absence of any reactions caused by central nervous stimulation, such as nervousness, tremor, apprehension, or insomnia.

PRESSOR ACTION

Observations on the pressor action of paredrine are relatively meager. Alles⁵ found that paredrine has a more intense pressor action than phenylisopropylamine (benzedrine). Abbott and Henry⁷ reported that paredrine is about twice as effective as ephedrine in raising blood pressure in man. Altshule and Iglauer⁸ concluded that paredrine was a more potent pressor drug than benzedrine, and found the compound of value as an adjunct in the treatment of the vasomotor collapse of hemorrhage, pulmonary embolism, and surgical shock.

In the present study, observations were made on fourteen subjects from the hospital wards. The measurements were made under basal conditions, in the postabsorptive state, with the subject in the recumbent position. Repeated observations were made under similar conditions. After several control blood pressure readings and pulse rate determinations, paredrine hydrobromide was administered. After a subcutaneous dose, usually of 20 mg., subsequent blood pressure readings were made at five, fifteen, thirty, forty-five, and sixty minutes. After an oral dose, readings were taken after fifteen, thirty, sixty, and ninety minutes. Fourteen subjects received the drug subcutaneously in 20 mg. doses. In nine instances, the compound was given by mouth in 40 mg. doses and in four cases in 80 mg. doses. Table II shows the average rise in arterial pressure, the maximum effect, and the duration of action.

TABLE II
THE RESPONSE OF THE BLOOD PRESSURE TO VARYING DOSES OF PAREDRI
IN NORMAL SUBJECTS

DOSE	AVERAGE RISE SYSTOLIC AND DIASTOLIC (MM. HG)	MAXIMUM RISE SYSTOLIC AND DIASTOLIC (MM. HG)	DURATION (MIN.)
20 mg. subcutaneously (14 cases)	51/16	73/30	40-75
40 mg. by mouth (9 cases)	52/17	106/42	60-120
80 mg. by mouth (3 cases)	69/24	82/33	120

In every case a sustained pressor effect was obtained. After oral administration this effect was noted within fifteen minutes in most instances, and the maximum effect occurred in thirty to sixty minutes. The duration of the pressor action after a dose of 40 mg. was sixty to ninety minutes, and, with the 80 mg. dose, one and one-half to two

hours. After the subcutaneous injection of 20 mg. the onset of action was within five to ten minutes, and the maximum effect occurred usually within fifteen to thirty minutes. The blood pressure returned to normal in most cases within an hour. The diastolic pressure was only slightly affected, as compared with the systolic pressure, but in no case was a lowering of diastolic pressure observed. There was also a marked variation in the intensity of the effect in different persons.

COMPARISON OF EFFECTS OF ORAL AND SUBCUTANEOUS ADMINISTRATION

One of the features which limits the usefulness of epinephrine is its instability and inactivity on oral administration. This applies to most of the sympathomimetic amines. In fact, the introduction of ephedrine was a great advance largely because it permitted the oral use of a sympathomimetic amine. In previous studies on cardiac standstill by one of us (M. H. N.), it was found that other hydroxyamines, such as tyramine, hordenine, synephrin, and neosynephrin, were ineffective on oral administration.⁴ In the present study it was found that paredrine retained a surprising degree of activity when administered by mouth. The following illustrates the comparative effectiveness by oral and subcutaneous administration:

TABLE III
AVERAGE BLOOD PRESSURE RISE

ORAL, 40 MG. (9 CASES)		SUBCUTANEOUS, 20 MG. (14 CASES)	
Systolic	52 mm.	Systolic	51 mm.
Diastolic	17 mm.	Diastolic	16 mm.

These observations indicate a complete or practically complete absorption and utilization of paredrine when it is administered by mouth. In one of the nine subjects to whom the drug was given by both routes, a relatively slight pressor effect was noted on oral administration as compared with the reaction after subcutaneous injection. This had been observed previously in the studies on cardiac standstill. In one case of heart block, 100 mg. by mouth failed to influence the ventricular rate or raise the arterial pressure. There is apparently an occasional case in which the drug is destroyed in the gastrointestinal tract, or there is incomplete absorption. A similar variation in activity has been observed after the oral administration of ephedrine.⁹ It is important to recognize this variation in activity for, in some instances, an effect may be obtained by increasing the average oral dose of 40 mg.; occasionally, the relative inactivity on oral administration makes the drug unsuitable for use by this route.

COMPARISON OF PAREDRIENE AND PAREDRIENOL (VERITOL)

Paredrinol, the N-methyl derivative of paredrine, has received a great deal of attention in the German literature under the name

"Veritol."¹⁰ A number of publications have appeared on the human and animal pharmacology of the drug, and it is claimed that this compound is a superior remedy in the treatment of circulatory collapse of various types. It is reported that the pressor action is mainly due to the emptying of venous stores of blood, and it has been suggested that the drug differs from other sympathomimetic amines which produce an increase in arterial pressure mainly by peripheral vasoconstriction. There is some difference of opinion as to the mode of action, and some question whether this compound differs fundamentally from certain other substances of this group.¹¹ In this country, Stead and Kunkel¹² concluded that the pressor action of paredrinol was due to one or both of the following mechanisms: (1) a direct vasoconstrictor effect on small blood vessels, and (2) a primary increase in venous tone, causing an increased venous return to the heart and a secondary rise in arterial pressure. In a recent study, paredrine and paredrinol were administered to a group of fifteen normal subjects subcutaneously and by mouth.¹³ In every instance paredrine produced a much greater pressor effect. Also, by either route of administration, the duration of the effect was definitely longer after giving paredrine (Table IV).

TABLE IV

MAXIMUM RISE IN BLOOD PRESSURE (IN MM. OF HG) AFTER EQUIVALENT DOSES OF PAREDRIENE AND PAREDRIENOL IN FIVE NORMAL SUBJECTS

		SUBCUTANEOUSLY, 20 MG.		ORALLY, 40 MG.	
		SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	Paredrine	18	3	32	12
	Paredrinol	9	2	14	8
2	Paredrine	36	6	57	12
	Paredrinol	22	2	58	6
3	Paredrine	54	8	90	19
	Paredrinol	20	1	14	0
4	Paredrine	52	22	46	14
	Paredrinol	22	6	46	0
5	Paredrine			96	17
	Paredrinol			66	24

EFFECT OF PAREDRIENE ON BLOOD VOLUME

Recently, observations have been carried out on the effect of paredrine on blood volume.¹² It has been claimed that continuous administration of epinephrine causes a reduction in blood volume and a condition resembling shock.¹⁵ Since paredrine has a prolonged sympathomimetic action, it seemed important to ascertain the effect of the drug on blood concentration and blood volume. The specific gravity of the blood was ascertained in six normal subjects by the Barbour and Hamilton falling drop method¹⁶ before the administration of the drug and at the height of the pressor effect. In no instance was any significant alteration in the specific gravity observed. In three cases the "Evans Blue" dye

method was used in the estimation of blood volume after the method described by Gibson and Evans.¹⁷ The dye concentration in the plasma was estimated with a photoelectric cell colorimeter. In each instance two control readings of dye concentration were made during the half hour preceding the administration of the drug. Readings were again made ten minutes after administering paredrine, at the height, and also at the end of the pressor effect. There was no significant deviation in the blood volume or any significant change in hematocrit readings after the administration of the drug.

PRESSOR EFFECT IN SPINAL ANESTHESIA

Various pressor substances have been used to counteract or prevent the fall in blood pressure which frequently accompanies spinal anesthesia. Epinephrine, ephedrine, neosynephrin, and benzedrine have been used for this purpose. Altshule and Gilman¹⁸ employed paredrine in fifty patients who developed a rapid and marked fall in blood pressure during spinal anesthesia. In every case the administration of paredrine was followed by a return of the blood pressure to a satisfactory level. In the present study,* observations were made on 114 patients who received spinal anesthesia. The drug was administered intramuscularly preliminary to the spinal tap, so that an interval of three to five minutes elapsed between the time the paredrine was given and the actual subdural injection of the anesthetic. Procaine hydrochloride was the anesthetic used in most cases. In eighteen, the operations were on the upper abdomen, and, in ninety-six, the surgical procedure was on the lower abdomen, prostate, rectum, or lower extremities. Fifty per cent of the patients were over 50 years of age. In ninety-five patients, or 83 per cent, the response could be described as satisfactory, in that a single pre-anesthetic injection of paredrine maintained a satisfactory blood pressure level throughout the operation. Of these, twenty-one received 10 mg., seventeen received 15 mg., and the remaining fifty-seven received 20 mg. of the drug. In eleven patients, or 10 per cent, the response could be considered as excessive, for a single pre-anesthetic injection elevated the blood pressure 50 mm. or more above the pre-anesthesia level. Two of these patients complained of severe headache. Two patients in this group received 10 mg. of the drug, and the remaining nine received 20 mg. In eight patients, or 7 per cent, a definite fall in blood pressure occurred during the operation. A second injection of paredrine promptly raised the blood pressure to a satisfactory level in each case, and this level was maintained throughout the operation (Table V).

After the experience with this group, the following method seemed satisfactory: a dose of 10 to 15 mg. of paredrine for low operations, and 20 mg. for operations on the upper abdomen. In an additional

*These observations were carried out by Dr. Julius Hersh, of the Department of Anesthesia, Cedars of Lebanon Hospital.

250 cases a satisfactory blood pressure level was maintained, and a second injection of paredrine was not necessary in any case. As compared with ephedrine, which had been used previously, it was found that a more satisfactory blood pressure level could be maintained more consistently, and that there were definitely fewer hypotensive reactions. In addition, paredrine proved much more efficient in restoring the blood pressure when it fell to a critically low level during spinal anesthesia.

TABLE V

THE PRESSOR ACTION OF PAREDINE IN EIGHT PATIENTS WHO SHOWED A DEFINITE FALL IN BLOOD PRESSURE DURING SPINAL ANESTHESIA

OPERATION	BLOOD PRESSURE BEFORE ANESTHESIA	PAREDINE MG. PRE-SPINAL (MG.)	BLOOD PRESSURE CHANGE DURING ANESTHESIA	PAREDINE MG. DURING ANESTHESIA (MG.)	BLOOD PRESSURE AFTER PAREDINE
Colostomy	160/110	20	190/120-80/60	10	120/80
Gastrectomy	110/82	20	140/ 90-80/40	10	160/70
Resection of colon	150/100	15	150/100-80/50	20	120/80
Transurethral resection	130/70	15	120/ 60-84/60	10	120/84
Cystotomy	158/112	20	120/ 90-80/70	20	150/100
Abdominal prostatectomy	145/84	10	160/ 80-80/60	20	140/80
Emergency cystotomy	50/40	20	120/ 80-50/40	10	100/80
Laparotomy for bowel obstruction	160/110	15	150/100-60/40	20	140/80

HEART RATE

Fourteen subjects received a subcutaneous injection of 20 mg.; the heart rate was increased in five (average, 11 beats per minute) and decreased in seven (average, 7 beats per minute). In two cases the rate was unchanged. Nine subjects received 40 mg. by mouth; there was an increase in the heart rate in three (average, 9 beats per minute) and in three there was no change. Four subjects received 80 mg. by mouth; the rate was decreased in three (average, 5 beats a minute) and unchanged in the other. It is usually stated that administration of the sympathomimetic amines is followed by a slowing of the heart rate, and that this relative bradycardia results from reflexes arising in the aorta and carotid sinus caused by the elevated blood pressure. However, Blumgart¹⁹ found an average increase of 16 beats a minute in eight of ten subjects after a subcutaneous injection of 0.5 c.c. of a 1:1,000 solution of epinephrine. Starr and his associates²⁰ noted, in six subjects who were carefully observed, a 21 per cent increase in pulse rate after the administration of 0.7 c.c. of a 1:1,000 solution of epinephrine and a 9.7 per cent increase in rate after ephedrine. Altschule and Iglaue²¹ observed a decrease in pulse rate after paredrine in three subjects and no change in two. Epinephrine increased the heart rate in the two cases which were studied. Keys and Violante²¹ observed, after the administration of neosynephrin, a definite bradycardia which lasted thirty

to ninety minutes, with pulse rates varying from 30 to 45 per minute. They concluded that the drug produces a primary bradycardia which is relatively independent of pressor reflexes over the vagus nerve. These observations indicate that the sympathomimetic amines may have a variable effect on the heart rate. It would appear that paredrine stands between epinephrine and neosynephrin; it causes less cardiac acceleration than the former, and less inhibition than the latter.

DISCUSSION

Since the isolation of epinephrine, in 1901, several hundred chemically related compounds have been synthesized and studied. However, only two substances, ephinephrine and ephedrine, have been widely used in therapeutics. Before the use of a new drug is suggested, it must be demonstrated that the drug has some advantages over the older compounds. Paredrine has a more sustained action than epinephrine, and its especial advantage is that it can be administered by mouth. As compared with ephedrine, paredrine is definitely more potent and is free of the unpleasant side actions which result from cerebral stimulation. As regards the effect on cardiac standstill, our observations indicate that all three compounds act in a similar manner; they have the property of increasing the activity of lower rhythmic centers, thus preventing cardiac arrest. The therapeutic indication is in conditions in which cardiac asystole may occur. In cases of heart block in which syncope attacks are frequent, ephinephrine is the drug of choice. In those instances in which attacks are infrequent, a drug which is effective on oral administration is desirable. Paredrine in doses of 40 to 60 mg. three times a day will usually increase ventricular rhythmicity, so that the tendency to standstill is lessened. The same therapy is indicated in patients who have syncope attacks associated with a hypersensitive carotid sinus.

As regards the pressor action of epinephrine and paredrine, there is evidence that there are differences in their mode of action, i.e., there is not only a quantitative but also a qualitative difference in their effects. Altschule and Iglauer⁸ found that the pressor action of paredrine was not associated with any increase in cardiac output, whereas there was a striking increase in cardiac output after epinephrine. These observers also noted a marked increase in the velocity of blood flow after epinephrine, but this did not occur after paredrine. Epinephrine usually lowers the diastolic pressure, whereas paredrine raises it. After the pressor response to epinephrine there is usually a hypotensive phase. This diphasic effect has not been observed with paredrine. Epinephrine constricts the minute vessels of the skin. Our observations indicate that paredrine dilates the small vessels of the skin. After an intradermal injection of paredrine we have noted a flushing of the skin, with an increase in skin temperature, whereas epinephrine always produces a zone of intense pallor. We have observed this difference when the drugs

are given subcutaneously. A flush of the skin, especially of the face, is noted often after the administration of paredrine, in contrast with the pallor observed after epinephrine.

It has been claimed that prolonged administration of epinephrine can reduce blood volume. No change in blood volume or specific gravity has been observed during the pressor action of paredrine.

These differences in mode of action are important in the application of pressor substances to therapy. In spite of the powerful action of epinephrine, its pressor action has found little practical application in therapeutics. In the most important hypotensive state, that of peripheral circulatory collapse, it is usually stated that epinephrine and related compounds are of no benefit and may be harmful. However, there is some difference of opinion on this point. Best and Solandt²² found that histamine shock, traumatic shock with hemorrhage, and traumatic shock respond favorably to treatment with a pressor substance and concentrated serum. Kabat and Freedman²³ reported experiments in which the slow administration of epinephrine maintained the blood pressure during and after intestinal manipulation, and observed an increase of 300 per cent in the survival rate. Favorable results have been reported in shock by the administration of ephedrine, neosynephrin, and paredrinol. Kunkel, et al.,²⁴ noted that paredrinol had a beneficial effect in the collapse which may be induced by sodium nitrite. We have observed symptomatic relief in orthostatic hypotension with a combination of benzedrine and paredrine. This has also been noted by Korns and Randall.²⁵ Stead and Ebert²⁶ found paredrinol useful in the treatment of circulatory collapse resulting from hemorrhage. It must be concluded that the exact status of the pressor substances in shock is not entirely settled. In surgical or traumatic shock these drugs should be considered only as adjuncts in treatment, but there is evidence that they may be of benefit in association with other measures. It should be pointed out that the differences in the action of epinephrine and paredrine would favor the latter drug in the treatment of shock. The more sustained effect of paredrine, the nonparticipation of the heart in the pressor action, the absence of any change in blood volume, and the dilating effect on the minute vessels of the skin are features which make this drug more applicable. In addition to the effects during spinal anesthesia, we have observed a definite and sustained rise in blood pressure, with clinical improvement, in circulatory collapse associated with a variety of conditions. Altschule and Iglaue²⁷ found that, with paredrine, they could restore the blood pressure to normal in Addison's disease and in shock caused by coronary thrombosis. They state also that the drug is a useful adjunct in collapse associated with hemorrhage, pulmonary embolism, and surgical shock. Although these observations are encouraging, the exact value of paredrine in shock must await the study of a large group of patients in shock, with observations on the circulatory dynamics before and after the administration of the drug.

CONCLUSIONS

Paredrine is a potent epinephrine-like compound which has a prolonged action and is effective on oral administration.

Paredrine is the most effective orally active compound in the prevention and treatment of cardiac standstill.

Paredrine produces a definite and sustained rise in arterial pressure.

The evidence available indicates certain differences in the mechanism of the pressor action of paredrine and epinephrine.

Paredrine is effective in the maintenance of satisfactory blood pressure levels during spinal anesthesia.

Although more data are essential, the drug appears to be of value in certain types of shock.

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DISCUSSION

DR. J. MURRAY STEELE, New York, N. Y.—I became interested in paredrine by the back door, so to speak, during a study of carotid sinus sensitivity. In the literature, and again today, the fact that there is no obvious central action of this drug was referred to. In attempting to sort out the varieties of carotid sinus sensitivity, that which is supposed to be cerebral in origin is quite regularly stopped—the convulsions are stopped—by the administration of paredrine, although they are not stopped by atropine.

I would like to ask Dr. Nathanson on what grounds evidence rests to the effect that there is no central action of this drug.

DR. S. P. SCHWARTZ, New York, N. Y.—I should like to ask Dr. Nathanson what effects the sympathomimetic drugs have upon the carotid sinus itself.

Secondly, I wonder if Dr. Nathanson could tell us how epinephrine hydrochloride is absorbed after its parenteral administration during standstill of the ventricles.

DR. WALLACE M. YATER, Washington, D. C.—Will Dr. Nathanson tell us whether maintenance of administration can be carried on and what the maintenance dose might be in the average case?

DR. IRVING S. WRIGHT, New York, N. Y.—Dr. Nathanson said that apparently in some instances the drug is not utilizable by mouth, whereas in other instances it is. I should like to ask him whether any studies have been made as to whether the drug is better utilized in an acid or alkaline medium, and, if so, whether he has found any comparison between in vitro and in vivo studies in that regard.

DR. CARL A. JOHNSON, Chicago.—These drugs, known as sympathomimetic drugs, may have both sympathetic and parasympathetic actions. This is especially true of neosynephrin HCl, for if 10 mg. are given subcutaneously to the unanesthetized human subject, a marked slowing of the heart rate results, which probably is a parasympathetic effect, and there is an increased peripheral vascular constriction from the sympathetic effect. Although these drugs are similar in chemical structure, their actions differ qualitatively and quantitatively.

I would like to ask Dr. Nathanson about the site of action of paredrine, just as the previous discussers have. Both ephedrine and epinephrine increase the irritability of the heart, and death from toxic doses is caused by ventricular fibrillation. Neosynephrin HCl, however, does not increase the irritability of the heart, and animals which die from toxic doses do not have ventricular fibrillation. In view of these differences in the action of these drugs on the heart, I would like to know whether paredrine increases the irritability of the heart, and also what the cause of death is when animals receive lethal doses.

As far as neosynephrin HCl is concerned, I take exception to the statement that this drug is not active when given by mouth. If large enough doses are given by

mouth on an empty stomach, a hemodynamic effect results, but the dose necessary to effect this is often in the toxic range (200 to 400 mg.). The dosage that produces this effect varies from patient to patient, and even in the same person. The oral use of this drug, therefore, is not practical.

DR. NORMAN E. FREEMAN, Philadelphia.—We have used paredrine hydrobromide in studies on the circulation in traumatic shock, and, in contradistinction to adrenalin, the pressor effects seem to be greater than the peripheral arterial constrictor effects. That may be one of the reasons why the administration of paredrine does not cause hemoconcentration and other evidences of reduced blood volume.

Kunkel, Stead, and Weiss, in their studies on paredrine, arrived at the conclusion that its effect was chiefly to produce constriction of the larger blood vessels, especially on the venous side, which would tend to mobilize the available blood volume. Experience in the treatment of low blood pressure from spinal anesthesia, and the low blood pressure which is associated with sudden interruption of vasoconstrictor impulses during the course of thoracolumbar sympathectomy would bear out these ideas.

I would like again to ask Dr. Nathanson what he thinks about its action on the various components of the vascular system, not only the heart, but also the great vessels.

DR. MORRIS H. NATHANSON.—I am glad to have these questions, for several of them were taken up in the portion of the paper that I did not have time to read.

In answer to the question whether paredrine possesses a central stimulating action, resembling that of benzedrine or ephedrine, I can definitely say that the drug has no such action in therapeutic doses. I have seen no such effect in any case; also, recently, it has been reported from Tainter's laboratory that the threshold dose for the central stimulating action in animals for benzedrine is 0.3 mg. per kilogram; for ephedrine, 5 mg. per kilogram; and for paredrine, 80 mg. per kilogram.

In answer to the question as to how the drug can be absorbed during cardiac standstill, the drug was not administered during the standstill. The procedure was to make a record showing the cardiac arrest. The drug to be tested was then administered, and, after suitable intervals, the carotid sinus pressure was repeated to ascertain whether the cardiac standstill could still be induced.

As to the question whether the presence or absence of gastric acidity may explain the variation in activity when it is given by mouth, I have no definite data on this point. I suspect that this is not the explanation. On the whole, the drug is well utilized when administered by mouth, but there is the occasional person who shows little effect after oral administration.

Dr. Johnson brought up several interesting points. As regards the parasympathetic effects of these compounds, the bradycardia caused by neosynephrin may be considered as such an effect, although I do not believe that this has been definitely demonstrated. Our studies on the effect on the heart rate would place paredrine between epinephrine and neosynephrin; the drug has less of a cardiac accelerating action than epinephrine, and also produces less cardiac inhibition than neosynephrin. As regards the effect of paredrine on the heart and blood vessels, I can see no evidence of any parasympathetic action.

I do not feel that the final answer on the mechanism of the pressor action can be given at this time. There is a rise in venous pressure, but it is doubtful whether the pressor effect is secondary to this action. The effect is probably chiefly one of arteriolar constriction. I feel from our studies that this statement is justified. My opinion is that the various sympathomimetic amines act alike in the prevention of cardiac standstill. The difference is only a quantitative one, and some are more effective than others. As regards the pressor action and the effect on the blood

vessels, there is not only a quantitative difference, but also a qualitative difference, especially between epinephrine and certain other substances of this group. For example, epinephrine, in its pressor action, increases cardiac output, accelerates blood flow, and produces pallor of the skin by constricting the small vessels. Paredrine apparently does not increase cardiac output or cause acceleration of blood flow. The effect on the blood vessels of the skin is entirely different. An intradermal injection of epinephrine produces pallor, with reduction of temperature, whereas a similar injection of paredrine causes redness and warmth around the site of injection. It is these and other differences which suggest that the objections to the use of epinephrine in shock may not apply to other sympathomimetic amines.

ISOLATED MYOCARDITIS

OTTO SAPHIR, M.D.

CHICAGO, ILL.

MYOCARDITIS, in general, is a rarely observed clinical entity which, as White¹ stated, can be diagnosed by the realization of myocardial involvement in infectious diseases, or, in a few cases, circumstantially by the discovery of acute heart block, abnormal electrocardiograms, etc. Christian² recently stressed that myocarditis, in the sense of an acute inflammatory process, is rare and of minor clinical importance. However, he continued, "if by acute myocarditis is meant the circulatory disturbances with or without evidence of degeneration of the muscle fibers or cellular infiltration between them, associated with infectious diseases, it is a frequent occurrence." It thus seems clear that the clinical concept of myocarditis is often linked with the physiologic disturbance in the circulatory apparatus, rather than with anatomically demonstrable inflammatory changes in the myocardium. One reason for this discrepancy lies in the fact that there is very little information obtainable for a correlation between anatomic changes in the myocardium and a clinical diagnosis of myocarditis. This may be explained in part by the fact that, during routine autopsies, as a rule only a few blocks are cut from the myocardium. The absence of inflammatory changes in these few sections certainly does not preclude a diagnosis of myocarditis, and a consequent report of a normal or degenerated myocardium often misleads the clinician, who expected a positive diagnosis to confirm his observations. That the diagnosis of myocarditis has fallen into discredit is, therefore, often definitely the fault of the pathologist who has failed to examine more representative blocks.

From a recent comprehensive review of the literature on myocarditis,³ it is apparent that actual myocardial inflammatory changes in the various diseases are not rarely described. Often, however, these changes are not mentioned in the diagnosis and only very rarely is myocarditis diagnosed clinically. Excepted from such a general conclusion is myocarditis in rheumatic fever, which, because of the characteristic microscopic picture, is often diagnosed anatomically and certainly often considered clinically. Also, paradoxically enough, in view of the fact that, as many pathologists believe, syphilitic myocarditis—in the absence of miliary gumma—cannot be recognized anatomically, so-called syphilitic myocarditis is often diagnosed clinically.

* From the Department of Pathology, Michael Reese Hospital, Chicago.
Aided by a grant from the A. B. Kuppenheimer Fund.
Received for publication Jan. 30, 1942.

There is a type of myocarditis—isolated, or Fiedler's⁴ myocarditis—which, during the last decade, has received increased attention simply because it is more or less diffuse and thus easily recognized anatomically, even when only a few sections are examined. Although this type of myocarditis seems relatively rare, it is interesting that, since attention was drawn to it in 1929,⁵ a number of reports have appeared in the literature, whereas until that time the condition was apparently little known in this country. More recent reports indicate that, if the clinician and pathologist alike are aware of this condition, not only the pathologist but also the clinician diagnoses the disease correctly. Therefore, it would seem likely that, from a review of the clinical and anatomic pictures of isolated myocarditis, some data concerning myocarditis in general might be forthcoming.

Fiedler's, or isolated, myocarditis is a special form of myocarditis, although it is not specific in the anatomic sense. Although Fiedler⁴ termed this myocarditis "acute interstitial," it is clear—as Šikl⁶ pointed out—that Schmorl, who studied the hearts in Fiedler's cases microscopically, actually described parenchymatous changes in some of the hearts, with outspoken necrosis. From a review of the reported instances, it appears that this type of myocarditis denotes more or less diffuse inflammatory changes in the myocardium, of wide variety and varied etiology; the principal thing that they have in common is isolated involvement of the myocardium by a nonspecific lesion, without inflammatory changes in the endo- and pericardium. Thus, rare instances of rheumatic myocarditis (Kramár⁷), in which there are Aschoff bodies without accompanying endo- or pericarditis, do not fall within the category of isolated myocarditis, nor are cases of pyemia with abscesses in the myocardium (suppurative myocarditis) included. There are also records of patients who died of heart failure, and, at autopsy, showed not only diffuse myocarditis, but also granulomas with necrosis and giant cells. Although some of these granulomas at first suggest a syphilitic or tuberculous etiology, neither tubercle bacilli nor spirochetes are present; however, sometimes there is a positive history of tuberculosis or of a syphilitic infection. This is referred to as granulomatous or productive myocarditis. But in the absence of any causative agents, if syphilis and tuberculosis can be ruled out, these granulomatous lesions may also be classified with "isolated myocarditis." Although extensive necrosis is not mentioned in many of the case reports of "isolated myocarditis" (Karsner⁸), the isolated involvement of the myocardium and the unknown origin would lead to the inclusion of this myocarditis as a subvariety of the isolated form.

There are other recorded instances of isolated myocarditis in which there were inflammatory cells, many of which were eosinophiles. The belief is expressed that this type of myocarditis may be of an allergic nature, perhaps resulting from a special idiosyncrasy to either bismuth

or arsenic compounds, although adrenalin has also been held responsible (Franz⁹). However, since only the myocardium is involved, with no changes in the endo- or pericardium, and since the other organs show no characteristic change, it seems wise to include these myocarditides also under isolated myocarditis, especially since the allergic nature of this lesion has not been proved.

Inasmuch as we were aware of the existence of isolated myocarditis and realized the importance of examining many blocks of the heart muscle in order to make a correct diagnosis, we routinely and carefully studied the myocardium in all cases in which the possibility of myocarditis was suggested, principally by evaluation of the autopsy observations, but also post hoc by certain clinical observations. As has been pointed out elsewhere, few data are available concerning the frequency of myocarditis in general autopsy material, and there is no information regarding the incidence of isolated myocarditis. Chudějová¹⁰ (1933), in reviewing autopsy material in 8,474 cases, mentioned 221 instances of myocarditis. However, since no details were given, it seems that certain instances of arteriosclerotic heart disease must have been included among the 221 hearts. Brown and Hunt¹¹ studied 113 instances of infectious diseases and found myocarditis in forty-six.

In 5,626 autopsy cases, routine examination of the hearts disclosed 240 instances of myocarditis. Not included in this material are contagious diseases and syphilis. Isolated myocarditis of the granulomatous variety, as discussed above, was encountered only once, and diffuse myocarditis fourteen times.

The following are some of the clinical data on thirteen patients, and a summary of the gross and histologic observations, showing inflammatory changes isolated in the myocardium. An analysis of these and other reported cases is presented with a view to clarifying this entity. The possible causes of isolated myocarditis are also discussed.

CLINICAL NOTES*

Since none of the patients was observed by the author, the most essential facts given here were taken from the clinical records. There were twelve instances of the diffuse type, with no circumscribed granulomatous lesions, and one which was characterized by the formation of granulomas. The twelve instances of myocarditis, although anatomically principally identical, may be classified as those in which neither clinically nor at autopsy were other lesions demonstrated which might be correlated with the myocarditis; and those in which other diseases were present, but, as far as could be ascertained, were not likely to have borne any causative relation to the myocarditis. Five of the twelve patients with the diffuse type of myocarditis had other diseases. One had Laennec's cirrhosis, and another, tuberculous osteomyelitis. Two other

*I am indebted to the members of the Department of Medicine of Michael Reese Hospital for the records of these patients.

patients died suddenly after an operation for ventral hernia and for carcinoma of the large intestine, respectively. A fifth patient had a nodular colloid goiter with toxic symptoms and died suddenly before a contemplated operation. Seven patients at autopsy showed no disease except the myocarditis. Only one of these seven patients gave a history of a "septic sore throat." None of the patients had been treated with either adrenalin or any arsenic compound.

The patient with granulomatous lesions in the myocardium died suddenly without a history even suggesting disease.

The ages of the twelve patients with diffuse myocarditis varied from 10 months to 55 years. There were eight males and four females. The clinical diagnosis of heart disease was made in only three cases, and myocarditis was not recognized in a single instance. The heart disease was diagnosed as pericarditis, coronary thrombosis, and mitral stenosis with insufficiency, respectively. On two of these three patients electrocardiograms were made, and the following changes were encountered (Dr. L. N. Katz): The first had a rate of 67 per minute. The P-R interval was 0.44 sec. QRS was upright in Lead I, inverted in Leads II and III, and slurred or notched in the limb leads, and the duration was prolonged to 0.16 sec. P was upright in Leads I and II and diphasic in Lead III. S-T₁ was depressed, and S-T₂ and S-T₃ were elevated. T₁ was inverted, and T₂ and T₃ were upright. The chest lead (Lead CF₂) showed that QRS was prolonged, almost entirely electronegative, and notched and small, with the first phase inverted; S-T was normal in contour, and the P wave was diphasic. Interpretation: Sinus rhythm, first degree A-V block, intraventricular block of the common type. A definitely abnormal record.

The electrocardiogram in the second case showed a ventricular rate which averaged 96. No P waves were seen; instead, there were oscillations in the isoelectric portion of the record which were irregular in spacing, amplitude, and contour (best seen in Lead I) and had a rate which averaged about 340 per minute. The QRS was tiny in the limb leads, and definitely notched and prolonged; its duration was 0.12 sec. S-T was isoelectric in Lead I and depressed slightly in Leads II and III. T was tiny in the limb leads, inverted in Lead III, upright in Lead I, and indiscernible in Lead II. In Lead III a bizarre, premature, ventricular complex was seen. The chest lead (CF₂) showed that QRS was almost entirely negative, S-T abnormally elevated, and T upright; at times there was an upright U wave. Interpretation: Fine auricular fibrillation, with a moderately rapid ventricular rate; a ventricular premature systole; intraventricular block of the indeterminate ("low voltage") type. A definitely abnormal record. Note: Toward the end of Lead I artifacts are present, causing instability of the base line.

In one of the cases in which heart disease was recognized clinically the heart was enlarged and a rough systolic murmur was heard over the

apex. Three days before death, evidence of cardiac failure was noted. The second patient was admitted with epigastric distress and was orthopneic and cyanotic. The heart dullness was diffusely enlarged, and there was a pulsus paradoxus. The cardiac borders did not shift with change of position. The clinical diagnosis was pericarditis. The third patient had had shortness of breath for some time. He was dyspneic and had palpitation. The apex beat was diffuse, and a systolic thrill was noted over the apex and over the pulmonic area. All these patients had in common a weak, rapid pulse and low arterial blood pressure. One had precordial pain. However, the progressive myocardial failure dominated the clinical picture.

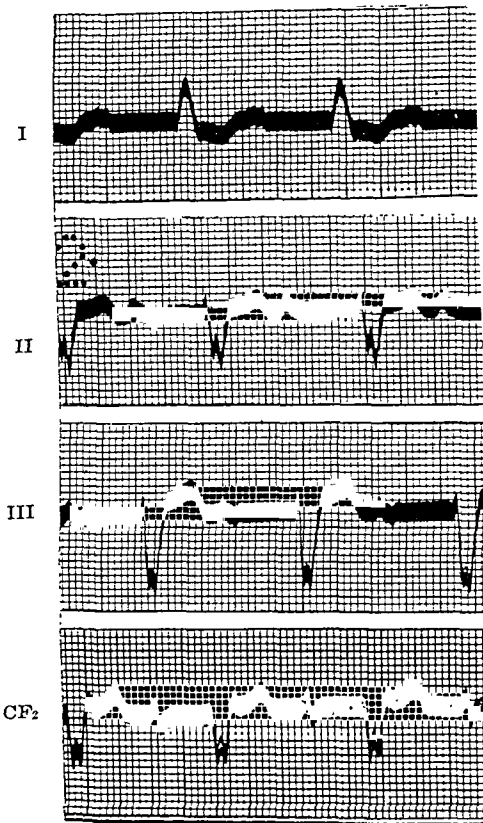


Fig. 1.

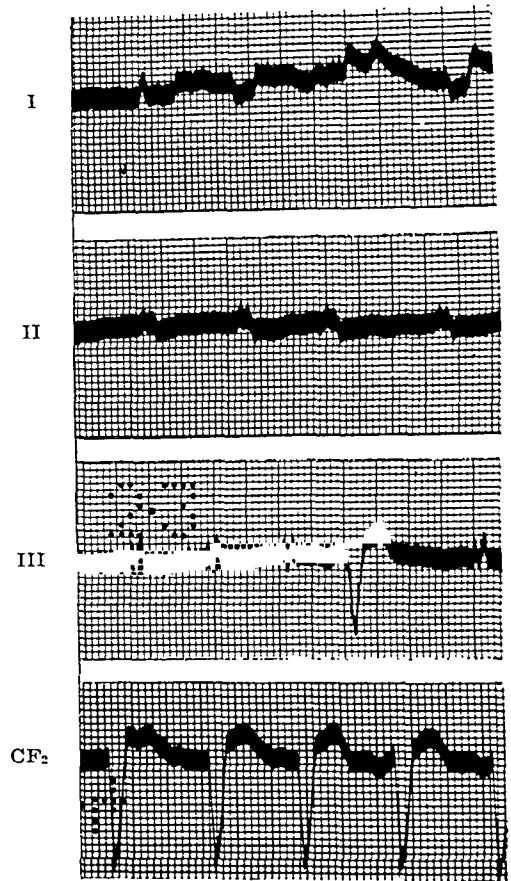


Fig. 2.

Nine of the twelve patients with diffuse myocarditis died suddenly. In one case death was attributed to coronary thrombosis. Two patients died unexpectedly after laparotomies. Three patients were brought to the hospital in extremis, were very cyanotic, and died before any history could be taken.

The patient who had granulomatous myocarditis, a 40-year-old man, had, as far as could be ascertained, never complained of any illness, but suddenly dropped dead while working.

ANATOMIC OBSERVATIONS

All of the hearts were enlarged and dilated. Neither the pericardium nor the endocardium showed any abnormalities. The myocardium was pale gray, and often faintly tinged with yellow, with minute grayish streaks or larger areas of gray and white which varied, but corresponded roughly to the relative age of the disease. Histologically, the lesions were diffuse and principally interstitial in location, although the heart muscle fibers were also involved. There were neither characteristic cellular accumulations nor did one particular type of cell predominate.

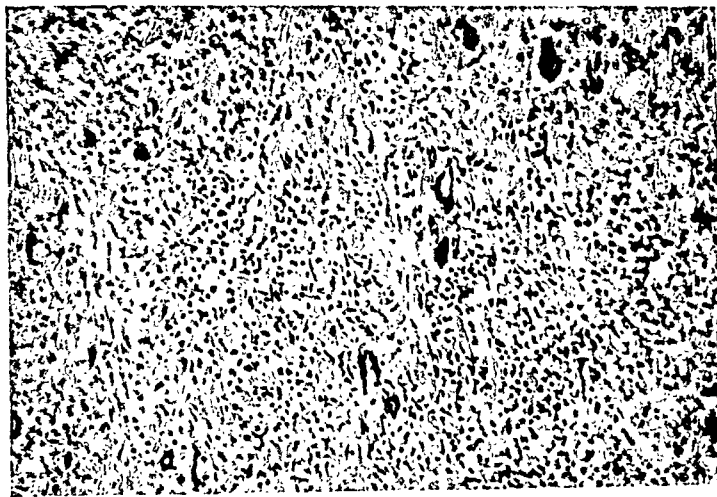


Fig. 3.—Granulomatous myocarditis. Note the giant cells, most of which are muscle giant cells. Hemotoxylin eosin preparation, $\times 130$.



Fig. 4.—Granulomatous myocarditis. Note the muscle giant cells. Hemotoxylin eosin preparation, $\times 280$.

Lymphocytes and endothelial leucocytes were the most commonly encountered cells, although polymorphonuclear leucocytes and eosinophilic leucocytes were also seen. Mast cells, which are normally found within

the interstitial tissue of the myocardium, seemed more numerous than usual. Transitions from the inflammatory cellular exudate to scar tissue were often encountered. Although often a perivascular distribution of the inflammatory cells was conspicuous, these accumulations never resembled those of rheumatic myocarditis.

The hearts of the three patients in whom heart disease had been recognized clinically showed many recent and old fibrotic lesions throughout the myocardium. Also present, however, were accumulations of lymphocytes and endothelial leucocytes.

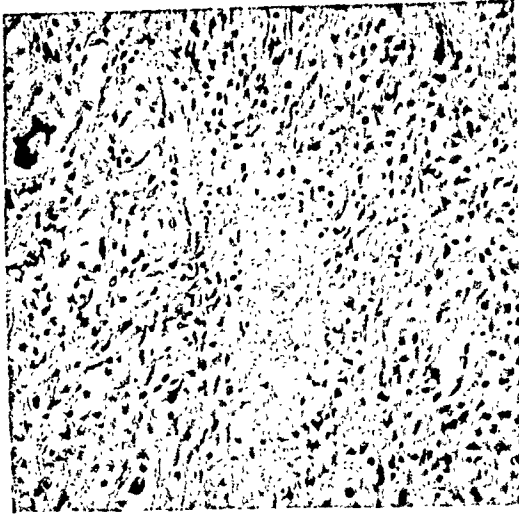


Fig. 5.—Granulomatous myocarditis. Note the central area of necrosis. Hematoxylin eosin preparation, $\times 200$.

The heart which was the seat of the granulomatous myocarditis was about normal in size. Throughout the myocardium there were many irregular, yellowish-white areas, about 3 mm. in diameter, occasionally somewhat larger, which showed a tendency toward fusion. In places they reached the endocardium and there assumed the form of minute nodules. The pericardium showed no change. Histologically, there were large areas of necrosis, at the periphery of which many lymphocytes, eosinophilic leucocytes, and a few endothelial leucocytes were encountered, but none of these cells predominated particularly. Conspicuous were a number of giant cells, with nuclear distribution more or less toward the periphery. Some of these giant cells were definitely not muscle giant cells, but resembled those seen in tuberculosis. In addition, however, many typical muscle giant cells were also encountered. Circumscribed areas without necrosis, consisting of lymphocytes, eosinophilic leucocytes, and a few giant cells, were numerous. These regions were richly vascularized, and the vessels had thin walls. The adjacent myocardium disclosed a diffuse infiltration predominately of eosinophilic leucocytes and lymphocytes. Neither spirochetes nor tubercle bacilli could be demonstrated.

COMMENT

From the data presented, it is clear that a form of myocarditis exists which is unaccompanied by either endocardial or pericardial lesions, and that it occurs in the absence of acute infectious diseases which are known occasionally to cause myocarditis. In ten of thirteen of these patients sudden death was attributed to the myocardial changes.

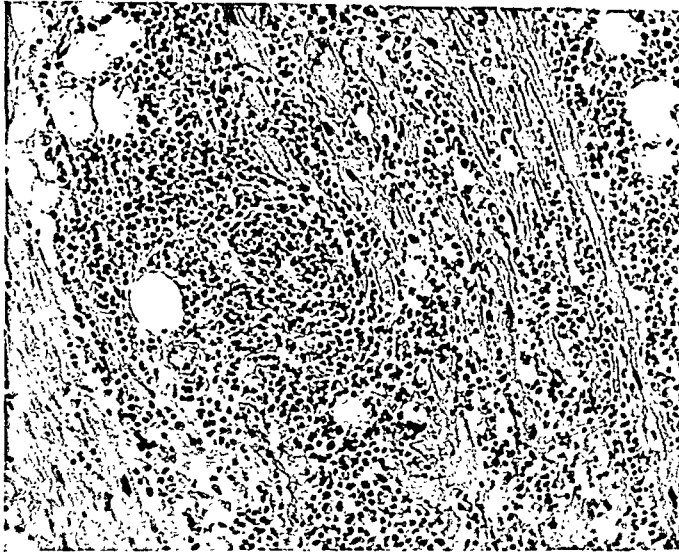


Fig. 6.—Diffuse myocarditis. Most of the inflammatory cells are lymphocytes. A few polymorphonuclear leucocytes are also present. Hematoxylin eosin preparation, $\times 150$.

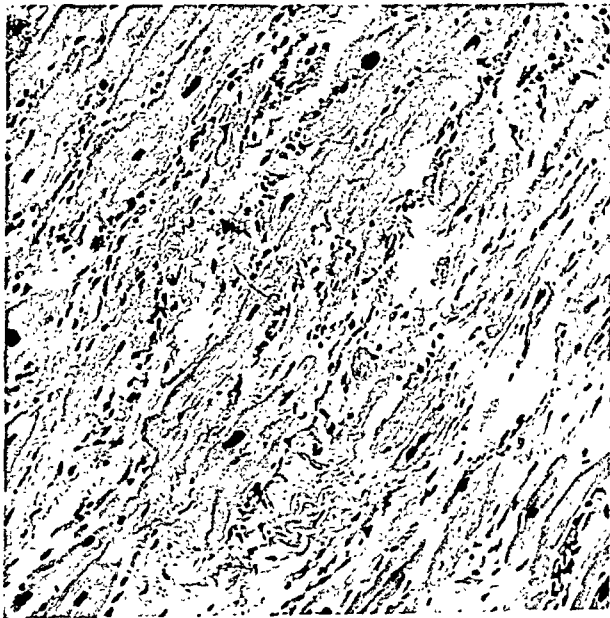


Fig. 7.—Old myocarditis. Note the fibrosis and the inflammatory cells. Hematoxylin eosin preparation, $\times 250$.

Diffuse myocarditis may easily be subdivided into the acute, fulminating form, which rapidly causes cyanosis and death, and a more protracted form. A subdivision has been made by Boikan,¹² who stated that

acute myocarditis, although it usually caused the death of the patient, might occasionally undergo healing, with much formation of new connective tissue. The patients in this series who died suddenly after surgical procedures, as stated above, and the three who were brought to the hospital in extremis apparently belong to this first group. The second group includes the truly chronic forms which invariably cause death after several months. The left ventricle, particularly, and occasionally also the left auricle, are involved in these instances. The initial changes, according to Boikan,¹² are round cell infiltrations; the cells either localize in groups, or more diffusely infiltrate the interstitial tissues. The capillaries are conspicuously dilated. He stated that, later, eosinophilic leucocytes are seen, and the muscle fibers become necrotic. Granulation tissue is formed gradually, and eventually foci of fibrosis replace the destroyed muscle fibers. The three patients in whom, as mentioned before, heart disease was diagnosed clinically, apparently belong to this group. The third group (Boikan¹²) is characterized by the simultaneous presence of recent and old inflammatory changes. Simon and Wolpaw¹³ reported such an instance. Because this is a progressive disease which culminates invariably in the death of the patient, with the clinical picture of progressive cardiac failure, the term "pernicious" was applied by Boikan.¹²

Progressive heart failure and rather sudden symptoms of congestive failure are often present in these cases. Simon and Wolpaw¹³ stressed progressive heart failure in their patient. Bailey and Andersen¹⁴ remarked on their patient's cardiac pain. Cyanosis, sometimes intermittent, is occasionally observed. It should again be emphasized that the diagnosis of myocarditis is rarely, if ever, made; the scant signs are misinterpreted as evidence of either coronary disease or pericarditis. Mitral disease is also an occasional premortem diagnosis. In children with symptoms referable to heart disease, toxic myocardial degeneration is most frequently diagnosed. An overlooked infection, possibly diphtheria, was suggested as a cause of myocarditis by Singer.¹⁵ The clinician is seemingly under a spell which prevents him from diagnosing myocarditis.

Changes are also reported in the electrocardiogram. De la Chapelle and Graef¹⁶ were apparently the first to find evidence of severe impairment of conduction in this disease.

Death from isolated myocarditis often occurs suddenly. In this series ten patients succumbed unexpectedly. The patients in Major and Wahl's¹⁷ series, who also probably fall in this group, died suddenly. Helwig and Wilhelmy¹⁸ stressed that interstitial (isolated) myocarditis should receive serious consideration in any case of sudden and unexpected death in which, at autopsy, naked eye examination reveals no anatomic lesion which could be held responsible.

The cause of isolated myocarditis is obscure; many possible factors have been considered, such as upper respiratory infections, "influenza,"

toxemias, and injuries of the myocardium brought about by such chemicals as sparteine and adrenaline. Recently, Chamberlain¹⁹ reported a patient with a history of alcoholism. It must also be emphasized that neither grossly nor histologically does isolated myocarditis vary in any essential from the myocarditis which is seen occasionally in the course of pneumonia and other acute infectious diseases, and in other conditions. Gouley, McMillan, and Bellet²⁰ described peculiar myocardial changes in pregnancy, but did not wish to imply that this form of myocardial change is specifically dependent upon pregnancy or on the puerperal state, because they had encountered it at least twice in men. They remarked that the clinical picture and the gross morbid anatomic changes in these cases were similar in many respects to those of Fiedler's myocarditis. Thus, the question arises whether or not one is justified in segregating Fiedler's myocarditis—perhaps excluding the granulomatous form—as a special type of myocarditis. The classification would not be based on the gross or histologic picture, but rather on clinical observations, absence of definitely known causes of myocarditis, and subsequent autopsy observations in those cases in which the clinical diagnosis was not made.

Isolated myocarditis also occurs in infancy and childhood. Two infants are included in Smith and Stephens'²¹ series. Lindberg,²² Blüh-dorn,²³ Maslow and Lederer,²⁴ Greenebaum, Felson, and Zeligs,²⁵ and Kenny and Sanes²⁶ reported relevant instances. It is interesting to note that Singer,¹⁵ who found myocarditis in two infants who died suddenly, suggested that it might have been caused by a clinically overlooked infection, possibly diphtheria. In our series three instances were found in children; they were 10 months, 15 months, and 3 years old, respectively.

The granulomatous form of isolated myocarditis is much more rare than the diffuse type. Again it may be emphasized that neither tubercle bacilli nor spirochetes can be demonstrated in these hearts, although a history of either tuberculosis or syphilis may be obtained (Taussig and Oppenheimer²⁷). However, in this respect mention may be made of Karsner,⁸ who stated that syphilis cannot be excluded because of a negative Wassermann reaction and the inability to demonstrate spirochetes. Earlier reports of this kind of myocarditis were made by Baumgartner,²⁸ Saltykow,²⁹ and Gierke,³⁰ and, more recently, Magner,³¹ Šikl¹⁶ (who reviewed the literature), Hansmann and Schenken,³² Jonas,³³ and Miller³⁴ reported relevant instances. In discussing Miller's case, Lillie³⁵ remarked that, in experimental tularemia, a granulomatous myocarditis which resembles the lesion in human granulomatous myocarditis is not infrequently found. This is interesting because the question immediately arises whether or not there may be other infectious diseases that also produce granulomatous lesions in which the causative organism cannot be demonstrated, and in which the granulation tissue is not

characteristic enough to lead to the recognition of the etiologic agent. Blastomycosis can be ruled out because it is easy to recognize blastomycetes in section. Sidorov³⁶ reported a case of granulomatous myocarditis caused by *Balantidium coli* and demonstrated the organism. However, trichinous myocarditis is one form which presents neither a characteristic nor pathognomonic histologic picture, and, apparently, trichinae are not found in the myocardium of the experimental rabbit later than eight days after the infection. Although in exceptional instances the larvae were found on the twenty-sixth and twenty-ninth day of the infection, they are, as a rule, not present in the myocardium, for patients usually die between the fourth and sixth week of the infection.

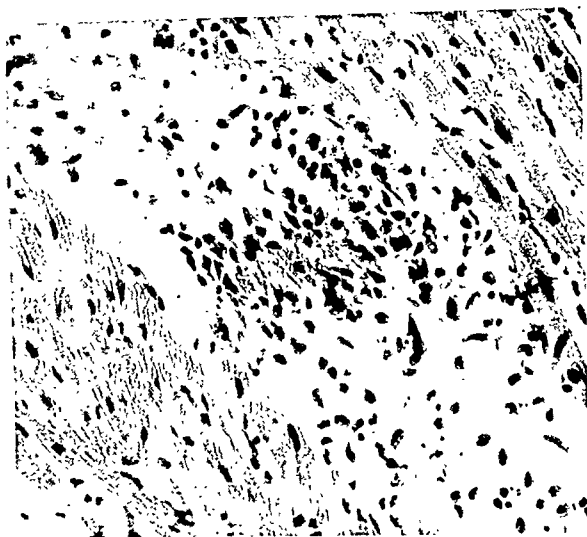


Fig. 8.—Trichinous myocarditis. Note the granulomatous lesion, with necrotic foci. The patient died in the fifth week of the disease. *Trichinella spiralis* was found in the diaphragm. Iron hematoxylin eosin, $\times 300$.

Histologically, the myocardium shows focal or diffuse infiltrations of neutrophilic leucocytes, lymphocytes, and a few mononuclear leucocytes and plasma cells. Usually many eosinophilic leucocytes are also present, although their absence is occasionally stressed, whereas, in isolated (Fiedler's) myocarditis, a predominance of eosinophiles is sometimes noted (Magner³¹). The muscle fibers are degenerated or actually necrotic. Since it is now known that the larvae are present in the heart, as a rule, only shortly after the infection, their absence does not preclude a diagnosis of trichinous myocarditis. In a personal observation, actual, small, granulomatous lesions were found in the myocardium in a case in which *Trichinella spiralis* was encountered in the diaphragm. Histologically, the changes in the myocardium resembled those which are seen in granulomatous myocarditis and in diffuse isolated myocarditis. Only the discovery of trichinae in the diaphragm prevented us from classifying this myocarditis among the isolated forms. Weller³⁷ also remarked on the similarity of these two conditions, and Libman³⁸ ques-

tioned the similarity of eosinophilic and isolated myocarditis, as reported by Smith and Stephens.²¹ Thus, it seems clear that if attention is focused on the heart only, not only trichinous myocarditis, but perhaps also other types, may well be confused with isolated myocarditis. On the other hand, the question must be raised whether or not, in some instances, isolated, particularly granulomatous, myocarditis may be the result of one of the known causes of inflammation.

There are instances on record (Rosenthal³⁹) of myocardial inflammation in which only on histologic examination were valvular changes demonstrable. Thus, it is evident that such cases do not fall within the category of isolated myocarditis, and the absence of valvular lesions must be confirmed by microscopic examination before a definite diagnosis, based on myocardial changes, can be made.

Rheumatic fever as the causative agent can be ruled out. There are instances on record of rheumatic myocarditis without endocardial or valvular involvement, but the lesions in rheumatic myocarditis are characteristic enough morphologically to rule out rheumatic fever as the etiologic agent. Although it has been suggested (Sacks⁴⁰) that diffuse infiltration of the myocardium may represent an exaggeration of the less conspicuous leucocytic collections which accompany the Aschoff body, this does not seem to be a likely explanation of the cellular infiltrations in isolated myocarditis.

In some instances of myocarditis the inflammation was diffuse, involving large fields, and in others, many small foci of subacute inflammation were present. It is more likely that the difference in such cases lies in the severity of the myocarditis, rather than that it constitutes a different type of myocarditis. The three types of myocarditis described by Boikan¹² are probably different stages of the same disease.

Lindberg's²² report of isolated myocarditis is noteworthy because of his suggestion that the initial changes may be of the serous myocarditis type, similar to those found by Wennekebach⁴¹ in the beriberi heart, and described by Rössle⁴² and Eppinger, Kaunitz, and Popper.⁴³ The serous exudate in this type of myocarditis stimulates connective tissue overgrowth, and myocarditis, with marked fibrosis, ensues. The myocarditis described by Lindberg,²² and also by Boikan,¹² may perhaps have shown a "serous" component in its initial stage. It is interesting that Eppinger, Kaunitz, and Popper⁴³ mentioned burns as possible causes of serous inflammation, and that there are reported cases of isolated myocarditis in which burns are suggested as the possible etiologic agent (Zuppinger,⁴⁴ and Kaufmann⁴⁵).

Lately there has been more and more discussion whether or not the myocarditis may be of an allergic nature, perhaps a result of a special idiosyncrasy to certain chemicals (bismuth, arsenic compounds, neosalvarsan, etc.). Šikl,⁶ Ueke,⁴⁶ Nelson,⁴⁷ Zalka,⁴⁸ and Brown and McNamara⁴⁹ reported such instances (see also Saphir³). Maxwell and

Barrett's⁵⁰ patient had a severe dermatitis, apparently caused by sulphur ointment. Bernheim-Karrer's⁵¹ patient (a 13½-month-old child) had severe eczema of unknown origin. Brown and McNamara⁴⁹ stated that "in the light of our present knowledge, therefore, the acceptance of the allergy hypothesis to explain the myocardial lesions of arspenamine dermatitis rests on the exclusion of other causes on morphologic grounds and on the compatibility of the lesions with those encountered in other types of known allergy." Franz⁹ suggested that the myocardial lesion which he had observed may have been the result of the administration of adrenalin, or possibly was caused by hypersensitivity toward adrenalin. French and Weller⁵² very recently described an interstitial myocarditis, with many eosinophilic cells, in the hearts of 126 patients whose sole common factor was that one or more of the sulfonamide drugs had been administered shortly before death.

These observations are interesting, but sufficient data are not available to permit any definite conclusion in regard to the origin of isolated myocarditis. Many more examples should be studied, not only for myocardial changes, but, in addition, complete autopsies, with careful microscopic examination of all organs, are essential to ascertain whether or not pertinent changes may be encountered in other organs, particularly muscles, liver, kidneys, and brain.

Isolated myocarditis is also described in cases of hyperthyroidism. One of the patients here mentioned, who showed evidence of hyperthyroidism, died suddenly before a contemplated thyroidectomy could be performed. Magner's⁵¹ patient, although he showed no symptoms of hyperthyroidism, died eighteen hours after subtotal thyroidectomy. However, in a study of the relation between thyroid disease and myocardial changes, it was concluded³ from the evidence on hand and from a review of the literature that there are no consistent inflammatory changes in the myocardiums of patients who died of hyperthyroidism.

SUMMARY

There is a type of myocarditis of unknown origin which is not accompanied by endo- or pericarditis. It occurs in patients who have no other disease that may be correlated with the myocarditis. This myocarditis may also be present in apparently healthy persons who, more or less suddenly, develop progressive myocardial weakness and succumb quickly. Clinically, the outstanding manifestations, in addition to the progressive myocardial failure, are a weak, rapid pulse, low arterial pressure, and an increase in the area of cardiac dullness. Precordial pain may be present. The disease occurs at any age, although young people seem more frequently affected. Therefore, arteriosclerotic heart disease can easily be ruled out. There is no history of rheumatic fever. The patients often die suddenly. Of thirteen patients in this series, ten succumbed suddenly. It seems that clinicians, for some reason, rarely, if ever, diagnose the myocarditis.

Anatomically, isolated myocarditis does not vary in histologic details from the myocarditis which is occasionally encountered in the course of acute infectious disease. A diffuse and a granulomatous type can be distinguished. The latter is much rarer, and morphologically somewhat resembles the granulomas of tuberculosis and syphilis. Histologically, many giant cells (muscle giant cells) are often recognized. The minute granulomas which are seen in trichinous myocarditis may also occur in isolated myocarditis. Although nothing is known as to the cause of either the diffuse or granulomatous form, it seems imperative in every instance to examine histologically other organs and structures besides the heart in pursuit of the causative agent, as in trichinosis, or, perhaps, tularemia. Lately, a hypersensitivity, particularly to arsenic compounds (arsphenamine and salvarsan), has also been regarded as responsible.

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A NOTE UPON MORE ACCURATE MEASUREMENT OF DIASTOLIC BLOOD PRESSURE

J. MARION READ, M.D., AND J. SEWALL BROWN, M.D.
SAN FRANCISCO, CALIF.

THE auscultatory method of measuring blood pressure has almost entirely replaced all other methods. The reason for the rapid and universal adoption of Korotkow's auscultatory method was that it furnished a means of measuring diastolic pressure, which could not be done by palpation.

THE ERROR IN MEASURING DIASTOLIC PRESSURE

Numerous studies have been made upon the reliability of blood pressure measurements, and the subject has recently been reinvestigated and summarized by Shock and Ogden.¹ A review of most of the published figures reveals that the probable error in measuring diastolic pressure is greater than it is in measuring systolic pressure. This arises apparently from two causes, as follows:

1. The systolic pressure, as measured by the auscultatory method, is subject to check by palpation, and although it usually reads four to ten points higher by the former method, nevertheless palpation furnishes a means of checking the accuracy of the systolic reading which is not available in measuring diastolic pressure. Observation reveals that this fact is too often forgotten, or neglected, by clinicians, although its usefulness was stressed many years ago by Kilgore² and others, and re-emphasized in the "Standard Method for Taking and Recording Blood Pressure Readings" adopted by the American Heart Association and the Cardiac Society of Great Britain and Ireland.³

2. Great uncertainty seems to exist regarding the point at which diastolic pressure should be read. Some believe that it should be read at the end of the third phase (change of sound), and others at the end of the fourth phase (disappearance of sound). Some life insurance companies ask for a recording of both these end points, and some mention a fifth phase. The committee of the American Heart Association which drew up the "Standards"³ recognized the difficulties, and also provided for two readings when the end points are not identical. This seems unnecessary, and the stand of Wakerlin⁴ upon this point is well taken because there can be only one diastolic pressure, and there are

From the Department of Medicine, Stanford University Service, San Francisco Hospital, Dept. of Public Health of the City and County of San Francisco.
Received for publication Jan. 12, 1942.

means of establishing this, as we will show, by utilizing other available means of reading the end point rather than relying solely upon auscultation.

A MEANS OF REDUCING THE ERROR

It is common knowledge that, throughout the range of pulse pressure, there is a definite oscillation of the mercury column, or of the needle of an aneroid instrument. As the pressure in the encircling cuff is increased, oscillation begins as soon as this pressure against the artery just exceeds the intra-arterial pressure at the end of diastole. The entrance of each pulse wave into the compressed segment of artery makes a sound, and it also increases the intra-arterial pressure, which is transmitted back through the compressing system into the indicator. This causes an intermittent oscillation which is usually about 1 mm. Hg at the diastolic (and systolic) end points.

Attention to these two points of change in amplitude of the movement of the indicator will convince anyone that they correspond to the same points at which the systolic and diastolic pressures are read by auscultation. In fact, it is possible to measure systolic and diastolic blood pressure with considerable accuracy by utilizing only this visual method.

EXPERIMENTAL TESTS OF THE METHOD

To ascertain the degree of accuracy attainable by this method, one of us (J. M. R.) recorded diastolic and systolic pressure by the visual method alone, and the other (J. S. B.) took the pressure by auscultation. The readings were made simultaneously upon 102 ward patients, omitting only those with cardiac irregularities. We used alternately a mercury and aneroid sphygmomanometer. The degree of correspondence between the auscultatory and visual (oscillometric) methods is shown in Table I.

TABLE I

FREQUENCY OF OBSERVED DIFFERENCES BETWEEN BLOOD PRESSURE MEASUREMENTS BY THE VISUAL AND BY THE AUSCULTATORY METHOD

DIFFERENCE (MM. HG)	0	2	4	6	8	10	12 TO 14	16 TO 18	20 AND ABOVE	NO. OF OBSERVA- TIONS
Diastolic	15	26	20	20	6	4	7	2	2	102
Systolic	28	15	12	19	10	5	6	6	1	102

In addition to the above means of showing the close correspondence between the results of the two methods of measuring blood pressure, we calculated, also, the coefficients of correlation for the two series of observations. For diastolic pressure the correlation coefficient was 0.95, and for systolic pressure it was 0.98. Since the coefficient of 1.0 indicates perfect correlation, these are extremely, almost unbelievably, high values. We therefore hasten to point out that, as with other statistical measures, certain factors influence them which are not evi-

dent in the measures themselves. In this case the very high correlation coefficients resulted partly from the great range of our data. The diastolic pressures ranged from 30 to 140, and the systolic, from 72 to 250 mm. of mercury. Very close agreement at both extremes of the diastolic and systolic series tended to raise the correlation coefficient materially. Also, it was observed, when tabulating the observations in order to calculate the correlation coefficient, that the scatter about the regression line was small (especially for systolic pressures), and, furthermore, that those which were read too high were balanced by an almost equal number that were read too low. This factor was very potent in raising the coefficients of correlation to the high figures obtained in this series of observations.

THE GREATER VARIABILITY IN READING DIASTOLIC PRESSURE

The amount of "scatter," or variability in a series of observations, can be expressed by the statistical measure known as the *standard deviation*. This measure was calculated for our data, and for the diastolic pressure readings gave values of 4.92 and 4.8 by the auscultatory and visual methods, respectively. The standard deviations for the systolic pressure readings were lower, namely, 4.33 for the auscultatory, and 3.96 for the visual, method.

We believe that the lower coefficient of correlation and the larger standard deviations for diastolic pressure are significant and constitute additional proof of the greater difficulty in measuring diastolic pressure. This point was further investigated by calculating the standard deviations for several series of blood pressure measurements.

The first is the published series of Wright, Schneider, and Ungerleider.⁵ In 1938, "to emphasize the need for a universal standardization of the methods used in the measurement of blood pressure," these investigators studied the blood pressure readings made by interns, postgraduate students, and attending physicians upon unselected patients at the New York Post-Graduate Hospital. The greatest variations were found in the readings of the postgraduate group; the least, in those of the attending physicians; and the interns' were intermediate. We calculated the standard deviations of the variations from the mean diastolic and systolic pressures for all three groups, sixty-eight observations in all. The standard deviation for diastolic pressure was 2.49, whereas it was only 2.1 for systolic pressure.

The second series of blood pressure readings (285 in number) was gathered in the past three years from three successive classes in physical diagnosis at the Stanford University Medical School. After being taught the technique of taking blood pressures, each member of a small student group took the pressure of a patient, or another member of the group, and recorded it independently. This was done with the subject lying, and then standing, so that each student had two opportunities

to measure each subject's pressure. The instructor (J. M. R.) also took and recorded the subject's blood pressure, and the average systolic and diastolic pressures were ascertained. The standard deviations from these means, in millimeters of mercury, when calculated for both pressures, were 3.94 for the diastolic and 3.05 for the systolic pressure.

This greater variability in reading diastolic pressure is also shown by the figures of Shock and Ogden,¹ which were obtained by having two observers listen through the same stethoscope. Hamilton, Woodbury, and Harper⁶ published figures which show that, in comparing the direct (cannula) with the indirect (sphygmomanometer) method, the diastolic readings obtained by the indirect method deviated more from the values obtained directly than did the systolic measurements.

DISCUSSION

All of the foregoing observations indicate clearly that diastolic pressure presents greater difficulties in measurement than does systolic pressure. Recognition of this fact prompted Smith⁷ to write: "The criteria for measuring diastolic pressure have been (and still are) variable among individuals and countries" (he probably had in mind the matter discussed in the third paragraph of this paper). He was discussing the reasons why life insurance companies do not require blood pressure readings for all applicants. Although the value of these data to the insurance companies was not minimized, he pointed out that an inaccurate measurement of the pressure was likely to be more misleading than none at all. It is not only true that "blood pressure is the third most important routine physiologic measurement that the modern physician uses with a fine degree of precision"⁸ (sic), but it is also true that it is the only quantitative measure of a physiologic function upon which life expectancy can be estimated by insurance companies.

Clinically, it is usually of little consequence if the blood pressure is not measured accurately, even when there is an error of 10 mm. Hg. This obviously is not true with respect to life insurance examinations, as all examiners and medical directors realize. Inability or failure to measure the pressure accurately is a matter of considerable monetary consideration to the companies, and of economic and social import to the applicant. In other fields the accurate measurement of blood pressure can become crucial, e.g., when it is required as part of a physical examination preliminary to acceptance for employment in either private or civil positions; most pertinent just now is its inclusion as part of the examination of selectees under the Selective Service Act of 1940. With upper limits of 90 and 150 for diastolic and systolic pressures, respectively, the mode of life of a young man for the next year or two may hang upon a few millimeters of mercury, depending on how his pressure is read by the examiner. No one's blood pressure is constant, but, nevertheless, an examiner should be able to measure it accurately

within 4 to 6 mm. That this does not seem to be the case was shown by Wright, et al.,⁵ in their study of the results obtained by groups of physicians who measured the pressure simultaneously. Their results, which could have been anticipated, are nevertheless a startling record of inability to obtain even approximate values in one of the most frequent clinical procedures.

In view, therefore, of this demonstrably greater difficulty in accurately reading the diastolic end point, it seems desirable to sharpen the auditory estimate of this point by the visual impression gained from noting the change in amplitude of oscillation of the indicator at the diastolic (and systolic) end points. In fact, it has been our experience that the blood pressure of certain persons is almost impossible to measure by auscultation, so that it is necessary to resort to the visual and palpation method to furnish the end points.

CONCLUSIONS

There is need for more accurate measurement of diastolic and systolic pressure, particularly the former, which is more difficult to measure than the latter. Coordinating the change in amplitude of oscillation of the needle or mercury column with the change in sound makes for greater accuracy.

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ACUTE CORONARY THROMBOSIS IN INDUSTRY

II. INDIRECT INJURIES FROM TOXIC GASES AND OTHER PHYSICAL AGENTS

HARRY D. LEINOFF, M.D.
NEW YORK, N. Y.

THE medical-legal importance of acute coronary occlusion in industry was discussed in a previous paper.¹ This study is concerned particularly with the reaction of the heart to indirect injuries caused by exposure to toxic fumes, electricity, infections, and foreign proteins.

The patients were workers (except Case 6) who applied for compensation benefits, believing that certain incidents which had occurred because of, and during the course of, employment had caused acute heart disease. The most common diagnosis was acute coronary occlusion, although a better diagnostic term would have been acute toxic myocarditis or coronary circulation insufficiency. These clinical impressions rested on a varying combination of first recorded medical observations, a careful history, the examination, the subsequent clinical course, and the electrocardiographic, roentgenographic, and laboratory findings.

It can be safely stated that in all injuries the amount of damage is usually in direct proportion to the offending force and that the physical status of an organ determines its response to trauma.

CASE REPORTS

CASE 1.—F. G., a 65-year-old porter, was found unconscious, having been overcome by fumes escaping from a leaking gas heater. He was given first aid and was put to bed, but he refused hospitalization. The diagnosis was acute monoxide poisoning. He complained of severe headaches, nausea, vomiting, and weakness. The following day a pulse arrhythmia and falling blood pressure were noted, without cardiac complaints. These findings were significant in view of a known asymptomatic essential hypertension. He was seen five days later with no complaints. The heart was enlarged to the left; the sounds were distant and lacked snap; the pulse rate and rhythm were normal; there were no signs of decompensation; the blood pressure was 120/70; and the retinal arteries were moderately sclerotic. Serial electrocardiographic tracings showed sinus rhythm, left axis deviation, and acute myocardial damage. He remained symptom free except for transient heart pains and made a good functional recovery.

Comment.—This man was in good clinical health although he had a known essential hypertension with some coronary artery sclerosis.

Received for publication Dec. 22, 1941.

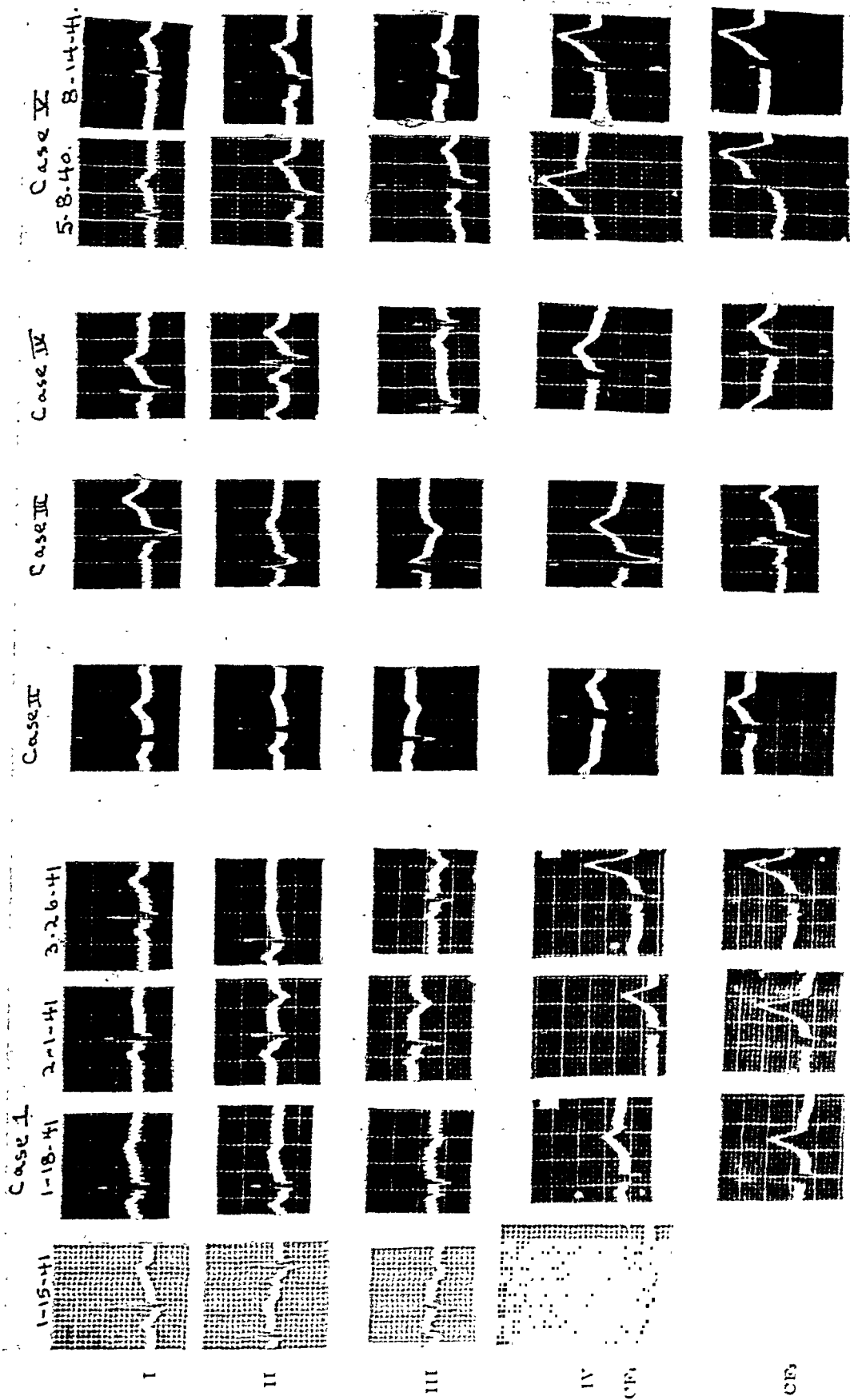


Fig. 1.—ECG positions same as suggested by American Heart Association.

After exposure to illuminating gas, he became unconscious and developed typical objective signs of acute heart damage within twenty-four hours. This sclerotic heart was probably damaged by the large dose of carbon monoxide.

Carbon monoxide combines with blood hemoglobin to form carboxyhemoglobin, a stable compound which interferes with oxygen absorption; this produces a relative asphyxia, thus placing an excessive demand on the heart.²⁻⁷ If this oxygen want is persistent, functional and organic changes may follow. In sclerotic and potentially diseased hearts more lasting and extensive damage may result. Drinker² and Beck^{3, 4} believe that an exposure to this gas may precipitate clinical disease. This case would tend to support this view. Many observers feel that, in addition to the anoxemia, this gas can produce an acute or subacute myocarditis with round cell infiltration,^{2-4, 6, 7} a lesion which has been demonstrated in experimental animals^{3, 4} and at autopsy.^{6, 7} In conclusion, it can be stated that carbon monoxide gas in fairly large doses can damage the heart by producing a toxic myocarditis or an acute coronary circulation insufficiency secondary to the oxygen want or by direct action on the coronary vessels.

CASE 2.—J. C., a 46-year-old truck driver, was forced to drive seventeen hours with closed windows during a bad spell of winter weather. At the end of this period, he became dizzy, felt a tightness across the chest, and had a severe headache. He stopped the car, opened the door, and lost consciousness. He was hospitalized with a clinical diagnosis of acute carbon monoxide poisoning, although no laboratory tests were performed to confirm this impression. While in the hospital he complained of precordial distress; rapid heart action and exertional dyspnea appeared when he was allowed to get up. The past history was normal. The patient did hard physical work without any difficulty on one job for eleven years.

He was seen seven months later with the same cardiac complaints. The heart was enlarged to the left; the sounds were of poor quality; the blood pressure was 130/100; the pulse rate and rhythm were normal; the response to exercise was poor; and the retinal arteries were moderately sclerotic. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and possible posterior coronary occlusion.

Comment.—This man was in good clinical health until he was exposed for a long period of time to an atmosphere containing a moderate amount of carbon monoxide gas. This resulted in typical symptoms of poisoning with an acute cardiac crisis. The mechanistic possibilities are the same as in the previous case except for the slow cumulative effect of a moderate concentration of the gas. The automobile engine is a very common source of this poison. Gettler and Mattice⁸ demonstrated that taxi drivers under ordinary working conditions may have as much as 6 per cent carboxyhemoglobin in the blood. There is little doubt that this patient absorbed a great deal of gas under the described working conditions.

CASE 3.—F. F., a 50-year-old automobile mechanic, was road-testing a car during a particularly cold spell with the windows closed. The floor boards had been removed, and gas fumes were seeping into the driver's compartment. At the end of an hour, he felt nauseous, faint, and dizzy and had a severe headache. He rested, but when he resumed his work, the same symptoms returned with a sense of chest pressure and rapid heart action. He was put to bed for ten days with a diagnosis of acute carbon monoxide poisoning; this was not confirmed by blood tests. On returning to work, he noticed that any contact with carbon monoxide resulted in cardiac symptoms which gradually became so bad that he was hospitalized. The past history was normal.

He was seen nine months later, complaining of exertional dyspnea and pain. The heart was normal in size, shape, position, movements, rate, and rhythm. The sounds were of poor quality and distant; a short systolic murmur was present; the blood pressure was 150/100; and the retinal arteries were moderately sclerotic. The response to exercise was poor. The electrocardiographic diagnosis was sinus rhythm, myocardial damage, and intraventricular heart block.

Comment.—F. F. was in good clinical health until he was exposed to a large dose of gas. Symptoms of monoxide poisoning and heart trouble resulted. He probably had an underlying sclerosis with silent myocardial changes, and this incident changed his clinical status.

CASE 4.—A. L., a 43-year-old laborer, attempted to remove two men who had been overcome by gas fumes while digging at the bottom of a deep shaft. In performing this task, he became faint, weak, and dizzy and lost consciousness. All three were finally removed by an emergency squad; the two workers died and only the patient survived. He was hospitalized with a diagnosis of acute "sewer" gas poisoning and myocardial damage. At this time he was unconscious and cyanotic and had a total cardiac arrhythmia which was considered auricular fibrillation, although no electrocardiograms were taken. He complained of rapid heart action, exertional dyspnea, precordial distress, severe headaches, nausea, vomiting, and abdominal pains. The past history was normal.

He was seen two and a half years later, complaining of weakness, exertional dyspnea, and cardiac pains. The heart was normal in size, shape, position, movements, rate, and rhythm. The sounds were muffled, and the blood pressure was 130/110. The electrocardiographic diagnosis was sinus rhythm, right axis deviation, and some myocardial damage.

Comment.—This man was in good clinical health until he was exposed to a mixture of gases which was toxic enough to kill two other men. He immediately presented cerebral and cardiovascular syndromes. This poison produced acute myocardial damage. The subsequent functional recovery did not parallel the objective findings, so that years later there were still complaints.

The offending substance was sewer gas, which is a combination of various hydrocarbons (such as methane), carbon dioxide, carbon monoxide, hydrogen sulfide, ammonia, nitrogen, and air. It is formed from decaying organic material and usually collects in pockets. The toxicity and symptomatology depends on the concentration of the various individual gases. These may replace the blood oxygen, causing asphyxia

with a resulting heart strain, or produce a toxic myocarditis. It is important to emphasize the toxicity of carbon dioxide, a substance which is usually considered nontoxic but which may be present in sewer gas in such high percentages as to be the lethal factor.

CASE 5.—W. R., a 21-year-old mechanic, stated that, while fixing an electric refrigerator, the sulfur dioxide tank exploded. He received chemical burns about the face, throat, mouth, and chest; local symptoms, cough, choking sensations, and a loss of taste and smell resulted. Several weeks later, exertional dyspnea, tachycardia, and weakness appeared. The past history was normal.

He was seen ten months later with the same cardiac symptoms. The heart and aorta were normal in size, shape, position, movements, rate, and rhythm. The sounds were of good quality; the blood pressure was 140/70; the response to exercise was normal; and the left cornea was scarred. The electrocardiographic diagnosis was sinus arrhythmia, no axis deviation, and some myocardial damage (precordial lead). Serial tracings subsequently were toward normal.

Comment.—This man was in good clinical health until exposed to a large dose of sulfur dioxide gas and liquid which caused severe local burns, exertional dyspnea, and tachycardia associated with changes in the electrocardiogram. The changes in the heart were of an acute nature and subsided with a good functional recovery.

Sulfur dioxide fumes irritate the respiratory mucous membranes, but when in contact with moisture change to sulfuric acid.^{5, 7, 9, 10} In severe poisoning, a secondary anemia and asphyxia cyanosis may follow.^{7, 10} The oxygen want is caused by either destruction of the oxygen absorbing membranes or the anemia which may follow. The anoxemia, if severe and prolonged, leads to structural and functional changes. The toxicity of sulfur dioxide gas, particularly as a refrigerant, was recently reviewed in an excellent study by McNally.¹⁰

CASE 6.—J. D., a 60-year-old housewife, was awakened from sleep by a severe attack of coughing, sneezing, difficulty in breathing, rapid heart action, and burning of the eyes and nose. This was caused by fumes escaping from a leaking sulfur dioxide tank in an electric refrigerator. She was kept in bed and subsequently complained of dyspnea and precordial distress. These symptoms had previously been present in a mild form, associated with a known hypertension.

She was seen about a month later with the same symptoms. The heart was enlarged to the left; the sounds had a fair quality with an accentuation of the second aortic; there was a rough systolic murmur; the retinal arteries were sclerotic; and the blood pressure was 250/110. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and possible coronary occlusion. Serial tracings, which were not obtained, would have helped to determine whether the changes were old or new.

Comment.—This case was included because the toxin was sulfur dioxide gas, although of a nonindustrial origin. The objective findings were inconclusive, but the increase of symptoms were suggestive of an additional loss of function. The presence of an underlying sclerosis often alters the response of an organ to trauma and may dictate the subsequent clinical picture.

CASE 7.—C. M., a 48-year-old tool maker, stated that his work consisted of hardening instruments by heating them in a chemical bath at temperatures ranging from 1,800 to 2,000° F. This procedure resulted in varying amounts of sulfur dioxide, hydrogen sulfide, nitrous and minute amounts of cyanide fumes which were ordinarily led off by proper flues. Following the installation of a new set of ovens with in-

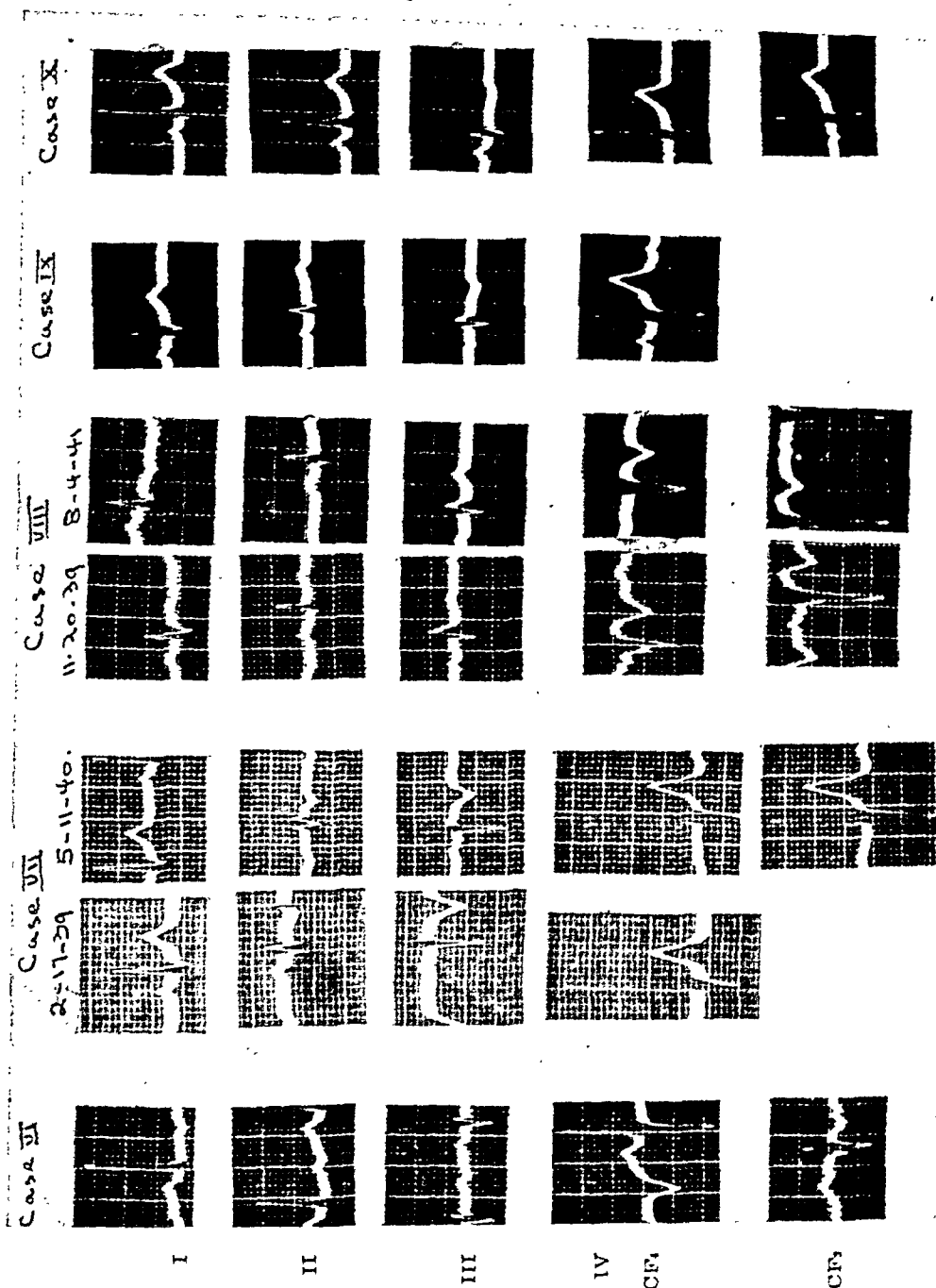


FIG. 2.

adequate ventilation, the patient developed nausea, headaches, dizziness, and rapid heart action. These symptoms recurred each time he used the furnaces, and on one occasion after ten hours of exposure he collapsed with a sense of pressure over the heart. He was put to bed with a diagnosis of acute coronary thrombosis. The past history was normal.

He was seen six months later, complaining of slight dyspnea. The heart was enlarged; the sounds were of fair quality; a soft apical systolic murmur was present; the blood pressure was 160/100; the response to exercise was normal; and the retinal arteries were moderately sclerotic. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and residual signs of a posterior coronary occlusion.

Comment.—The patient began to have complaints after the installation of a new set of furnaces with improper ventilation. These symptoms were persistent, and following an unusually long exposure he had a cardiac breakdown. This may have been a coincidence, but, in view of the fact that some of these gases can affect the structure and function of the heart, it seems probable that this contact under adverse conditions may have played an etiologic role in a heart already weakened by sclerosis.

CASE 8.—S. B., a 45-year-old stevedore, punctured his left arm with a cargo hook. The laceration was sutured; an injection of tetanus antitoxin was given; and he was sent home. Within twenty minutes he was aware of extremely rapid heart action and felt weak, dizzy, and chilly. These symptoms persisted; dyspnea developed and in six hours became so bad that he was put to bed with a diagnosis of an acute coronary occlusion. Four days later he developed joint pains, and a diffuse rash appeared. The acute picture gradually subsided. The past history was normal.

He was seen four months later, complaining of exertional dyspnea, cardiac pains, choking spells, and weakness. The heart was enlarged to the left; the sounds were of poor quality; a systolic murmur was present; the blood pressure was 152/110; the response to exercise was poor; and the retinal arteries were moderately sclerotic. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and anterior coronary occlusion.

Comment.—This man was in good clinical health until he lacerated his arm and received an injection of tetanus antitoxin. Within twenty minutes he developed signs of an allergic reaction with cardiac complaints, which in six hours warranted a diagnosis of occlusion. Was the heart collapse a mere coincidence, did the reaction to the foreign protein make an excessive demand on his sclerotic heart, or did the heart itself take place in the general allergic reaction. It is impossible to know the actual course of events, but cause and effect were too closely related to be considered an unqualified coincidence. A similar reaction following pneumococcus serum was recently reported.¹¹

CASE 9.—S. A., a 46-year-old theatre manager, received a face scratch in a fight. This break of the skin became infected, and within forty-eight hours he developed typical signs and symptoms of erysipelas with a temperature of 104° F. On the fourth day, at the height of the infection, he complained of heart pain, cough, sore throat, and extreme difficulty in breathing. At this time the objective findings were cyanosis, dyspnea, tachycardia, poor heart sounds, and numerous basal râles. He made a gradual recovery. The past history was normal.

He was seen four months later complaining of moderate exertional dyspnea, precordial distress, weakness, and some ankle edema. The heart was enlarged to the left; the sounds were of poor quality; there was a slight pitting edema; the re-

sponse to exercise was poor; and the blood pressure was 104/80. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and digitalis therapy.

Comment.—This man developed erysipelas, and at the peak of the infection signs and symptoms of an acute cardiac breakdown with decompensation appeared. This was caused by an acute infectious myocarditis, or the excessive heart demand, which was prolonged, led to a steady depletion of the cardiac reserve, ending in clinical failure and coronary insufficiency. The primary infection played an indirect etiologic role in the heart picture.

CASE 10.—M. H., a 46-year-old beauty parlor operator, accidentally short circuited a drying machine, causing the electric current to pass through her body for several minutes before she was released. She was unconscious for about fifteen minutes and then complained of rapid heart action, nausea, frequency of urination, severe headache, and a burn of the heel caused by the exit of the current. She was kept in bed for several weeks and, on getting up, noticed exertional dyspnea, precordial distress, weakness, and dizziness. The past history was normal.

She was seen three months later, complaining of mild dyspnea and heart pains. The heart, blood pressure, and electrocardiograms were essentially normal.

Comment.—This woman was in good clinical health until she sustained a severe electrical shock. She then developed signs of cardiac insufficiency without objective findings. She made a good functional recovery. The accident caused a loss of efficiency which was only temporary in nature. This case is in keeping with current reports. Gonzales⁷ feels that this type of injury may temporarily depress the respiratory and cardiac centers in the brain.

SUMMARY AND CONCLUSIONS

This is a clinical study of ten cases of acute heart disease following such indirect industrial accidents as exposure to toxic gases (Cases 1 to 7), electric current (Case 10), systemic infections (Case 9), and injection of tetanus antitoxin (Case 8). The term indirect means that the offending force is not applied directly to the heart, but acts in a remote and indirect manner. Each of these cases must be evaluated on an individual basis although certain well-defined general principles must be followed.

The functional and structural damage is usually in direct proportion to the offending force, and the response of an organ to trauma is dictated by the underlying physical condition.

Certain gases are capable of affecting the heart both in the laboratory and at the bedside. They may act on the heart by producing a toxic myocarditis, interfere with normal oxygen absorption by destruction of the mucous membranes of the lung, form stable compounds with the hemoglobin, produce anemia, or displace the oxygen in the blood. Oxygen want results in an excessive demand on the heart which, if pro-

longed, is followed by structural and functional changes. Systemic infections and foreign proteins may also make excessive cardiac demands. Electrical shock produces a dysfunction without organic changes. In gas poisoning, blood tests should be done to determine the qualitative and quantitative character of the toxin. The toxic action of gases depends upon the concentration and length of exposure. It is doubtful if a casual, isolated contact can produce serious heart damage unless the gas is very concentrated. In most of the cases, symptoms appeared after toxic doses of gas had been inhaled or the heart had been subjected to a sustained demand (Cases 8 and 9). The functional evaluation may often be delayed because the patient is bedridden.

The most important factors in establishing causal relationship were the history and the circumstances surrounding each incident. Every effort should be made to check the patient's story in order to arrive at a fair clinical conclusion.

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A PHONOCARDIOGRAPHIC STUDY OF THE HEART SOUNDS IN ACUTE CORONARY OCCLUSION

ARTHUR M. MASTER, M.D., AND RUDOLPH FRIEDMAN, M.D.
NEW YORK, N. Y.

SINCE Herriek's¹ classical description of coronary occlusion in 1912, impairment of the heart sounds has maintained an important place in the diagnosis of this condition. Its clinical significance was re-emphasized by Levine² but, in spite of the fact that excellent sound recording devices are available at present, the character and mechanism of the changes in the heart sounds have been studied phonocardiographically only by Parsonnet and Hyman³ and Master, Dack, and Jaffe.⁴ Until now the phonocardiograph has been used almost exclusively in the study of murmurs and the mechanism and physiology of the heart sounds, with scarcely any attempt to investigate the alterations of the heart sounds in the different types of heart disease and to correlate them with the clinical findings. We have therefore carried out such a study, beginning with acute coronary occlusion, preliminary results of which have already appeared.⁵

MATERIAL AND METHOD

This report is based upon observations in seventy-eight patients admitted to the hospital with acute coronary occlusion. Phonocardiograms were taken daily during the first two or three weeks and thereafter at least twice a week, until discharge from the hospital. At the time of these observations the heart sounds had not been recorded in normal persons of the same age group with the type of electric amplifying and filtering system we used. Since the inherent frequency characteristics of different sound recording devices have a varying modifying influence upon the recorded heart sounds, we collected our own control series of phonocardiograms in 100 normal persons over 40 years of age. In this age group the transmission of the heart sounds is modified by changes in the elasticity of the lungs and the thoracic cage, and the incidence of third heart sounds and auricular sounds is less than in younger persons.

The heart sounds were all recorded at the apex since it is generally the point of maximum audibility. The patient was told to hold his breath without strain at the end of a normal expiration; this excluded any effect of respiration on the intensity or pitch of the heart sounds. Phonocardiograms were always taken in the semirecumbent position to avoid

From the Cardiographic Laboratory and the Medical Services of the Mount Sinai Hospital, New York.

Received for publication Dec. 2, 1941.

possible changes due to differences in body position. The instrument used was an electric amplifying and filtering system,* the mechanics and structure of which have recently been thoroughly discussed by Rappaport and Sprague.⁶ We employed two microphones of different filtering range. The first transmits all the frequencies present in the heart sound, including those below the threshold of audibility, i.e., below 35 to 40 cycles per second. The second transmits only the higher frequencies, those usually audible to the human ear. We were thus able not only to study the different frequency elements of the heart sounds but to record them as they are actually heard during auscultation.

The volume control provided in the phonocardiograph made it possible to maintain the same degree of amplification in the serial tracings of each patient. Changes in intensity, particularly those of the first sound, could thus be followed with more accuracy than had been possible previously. Sometimes, however, this principle of uniform amplification could not be adhered to strictly, due to marked and rapid changes in the intensity of the heart sounds from day to day. If they became too faint, it was necessary to increase the amplification to obtain a record suitable for the study of frequency changes. If the sounds increased markedly in intensity, the amplification had to be reduced lest the base line lose its smoothness and become distorted by vibrations set up by sounds impinging too strongly on the microphone.

Simultaneous electrocardiograms and often also simultaneous venous pulse tracings were recorded since phonocardiograms without reference tracings may lead to false interpretation of the timing and identification of the heart sounds. Orías and Braun Menendez⁷ have demonstrated the value of venous pulse tracings particularly for identifying the sounds which occur in diastole, during which the electrocardiogram merely shows an isoelectric interval. The electrocardiogram is therefore of little aid in differentiating an auricular from a third sound and the latter from a split second sound, particularly in the presence of tachycardia. Moreover, the time relationship of the onset of these sounds to the T wave or to the P wave of the electrocardiogram depends too much on the heart rate to assure their accurate identification. Their relation to the waves of the venous pulse are much more constant; the third sound coincides with the descending limb of the "v" wave and the auricular sound coincides with, or slightly precedes, the peak of the "a" wave.

RESULTS

NORMAL CONTROLS

Before describing the phonocardiographic findings in the patients with acute coronary occlusion, we shall briefly present the observations in the group of 100 normal subjects, ninety-three of whom were over 40 years old and none under 32.

*Sanborn Stethocardiette.

1. *First Heart Sound: Amplitude.*—This is merely the graphic recording of the intensity of the sound and varies normally with such extracardiac factors as the elasticity of the thoracic cage and lungs, the amount of lung tissue interposed between the heart and the chest wall, and the amount and consistency of breast tissue. All these introduce difficulties in transmission, resulting in diminished amplitude and in changes in pitch of the heart sounds. Under favorable conditions of conduction the normal first heart sound shows the following configuration (Fig. 1): one or two vibrations of very low amplitude and frequency

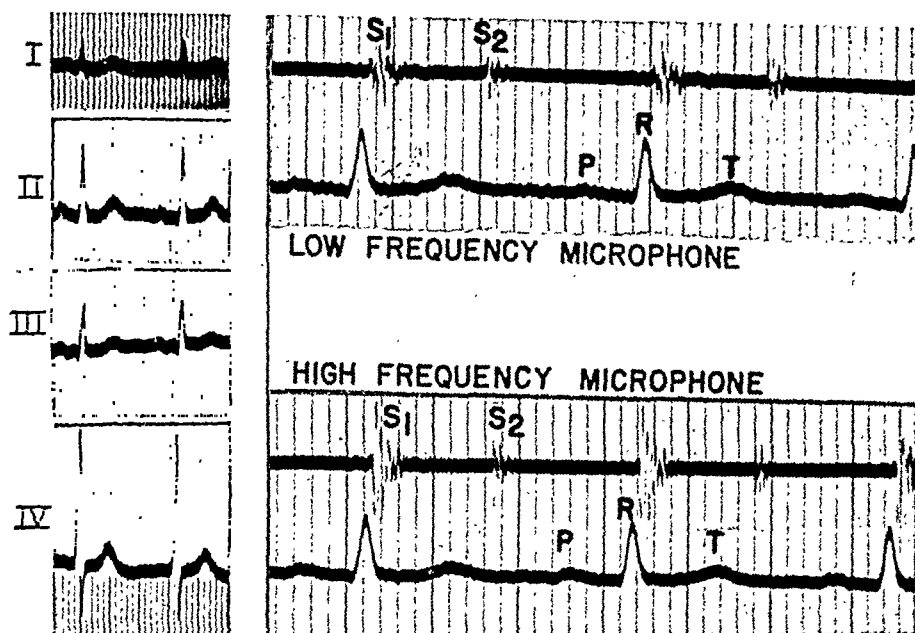


Fig. 1.—S. B. Normal male, aged 48, with normal electrocardiogram and phonocardiogram. The first sound (S_1) is of higher amplitude than the second (S_2) and central high-pitched vibrations. S_2 is of lower amplitude than S_1 . In this and the following figures strips of the four-lead electrocardiogram are shown on the left and the phonocardiogram with simultaneous Lead II on the right.

followed by a central group of vibrations of very high amplitude and frequency and finally one or two groups of vibrations of gradually decreasing amplitude. It has been established that the initial low component is auricular in origin and is caused by vibrations which continue from the auricular systole into the ventricular systole. The central group originates during the isometric contraction phase of the ventricles associated with a steep rise in intraventricular pressure. Whether it is produced by contraction of the ventricular muscle or, as many hold, by closure of the atrioventricular valves, has not been determined but is not relevant to this study. It is sufficient to emphasize the fact that these central vibrations occur during the isometric contraction phase and are therefore closely associated with the magnitude of the intraventricular pressure. The final groups of vibrations are set up during the ejection phase of the ventricular systole.

The configuration of the first heart sound just described was observed in the entire control series. Diminution in amplitude was found in six subjects (Table I). Since it affected all the components of the sound equally, it may be ascribed to extracardiac factors.

TABLE I

THE HEART SOUNDS IN SEVENTY-EIGHT CASES OF ACUTE CORONARY OCCLUSION
(Comparison With 100 Normal Subjects of the Same Age Group)

HEART SOUNDS	CORONARY OCCLUSION (%)	NORMAL SUBJECTS (%)
First Sound (S_1)		
S_1 low	24	6
S_1 lower than S_2	51	6
Auricular Sound (A_1)		
Total number	53	38
A_1 of normal amplitude	50	38
A_1 accentuated (presystolic gallop)	33	0
Third Sound (S_3)		
Total number	47	12
S_3 of normal amplitude	38	12
S_3 accentuated (protodiastolic gallop)	9	0
Summation Gallop (fusion of A_1 and S_3)	6	0

TABLE II

ANALYSIS OF THE FREQUENCY COMPONENTS OF THE FIRST SOUND
(Comparison of Thirty Patients With Coronary Occlusion With Thirty Normal Subjects)

	LOW-FREQUENCY MICROPHONE		HIGH-FREQUENCY MICROPHONE	
	CORONARY OCCLUSION	NORMAL SUBJECTS	CORONARY OCCLUSION	NORMAL SUBJECTS
Duration (sec.)	0.09	0.10	0.08	0.07
No. of vibrations	8.9	8.9	9	8.9
Frequency				
Average	82	83	118	116
Range*	60-100	60-100	80-140	80-140

*In 30 per cent of cases; in remaining 10 per cent the frequency was slightly beyond this range.

Table II presents the number of vibrations, duration, average frequency and frequency range of the heart sounds in thirty of the 100 normal subjects with tracings recorded by both the low-frequency and high-frequency microphones. A comparison of our figures with those in the literature, as compiled by Orías and Braun Menéndez,⁷⁻¹² shows close agreement in regard to the duration of the first sound but a slight, though definite, disparity in the average frequency range. This may be explained by a difference in the methods used, for our figures agree with those obtained by authors who also employed an electric amplification system^{13, 14} but are higher than those obtained by the direct mechanical methods of Wiggers and Dean.^{11, 12, 15, 16} We therefore accepted our own control phonocardiograms as normal. It is also evident in Table II that the vibration frequencies obtained with the high-frequency microphone were higher than those recorded with the low-frequency microphone, proof of the selective quality of the former type of microphone.

2. *Second Heart Sound*.—The second heart sound is of shorter duration and lower amplitude than the first. The first sound presented a higher amplitude in ninety-four of the normal adults over 40 years of age. In the remaining six cases the second sound was higher relative to the first sound and two of these six showed an absolute increase.

3. *Auricular Sound*.—An auricular sound (Fig. 1) was present in 38 per cent of the normal subjects (Table I), an incidence similar to that reported by others.^{12, 13, 17-19} The auricular sound usually consisted of one or two vibrations of low frequency (25 to 40 cycles) and amplitude, immediately preceding the first heart sound.

4. *Third Sound*.—A third sound (Fig. 1) was noted in 12 per cent of the control cases, the expected incidence in this age group. Its incidence has been found to fall with increasing age, being present in 57 to 95 per cent of adolescents and young adults²⁰⁻²² and in only 14 to 20 per cent of older persons.^{20, 23, 24} The configuration of the third sound (usually 1 vibration), its low frequency (25 to 35 cycles) and amplitude, and its relation to the second heart sound (approximately 0.10 sec. later) were similar to those generally described.^{12, 14, 18, 19, 25}

5. *Gallop Rhythm*.—Gallop rhythm was never encountered in the group of control subjects, since accentuation of the auricular or third sound, which produces this abnormality, does not occur in normal adults.

MYOCARDIAL INFARCTION

1. *First Heart Sound: (a) Amplitude*.—The amplitude of the first heart sound was absolutely low in 24 per cent of the seventy-eight patients (Table I); relative to the second sound it was low in forty-two cases (54 per cent), a very much higher percentage than was found in the control group (6 per cent). This reversed relationship of the amplitude of the first and second sounds, although known to the clinician, has been studied phonocardiographically only by Parsonnet and Hyman³ and by Master and his associates.^{4, 5} As a rule, the loss of amplitude affected the central group of vibrations which normally shows the highest amplitude and frequency (Figs. 2 and 3).

The diminution in amplitude of the first heart sound usually appeared immediately after the attack; in five of the forty-two cases the alteration took place in three to ten days. The abnormality usually persisted during the period of observation of three to nine weeks but in eight patients who survived normal amplitude reappeared in one to five weeks.

(b) *Frequency and Duration*.—In Table II it will be seen that there was no significant difference from the values found in the control phonocardiograms in the number of vibrations, the duration or the average frequency range of the first heart sound at any time during the attack. The essential difference was the decrease in amplitude of the central group of highest frequencies (Figs. 2 and 3).

2. *Second Heart Sound*.—We have just pointed out that forty-two of the seventy-eight patients with acute coronary artery occlusion presented a diminished first sound. As a result the second sound appeared louder

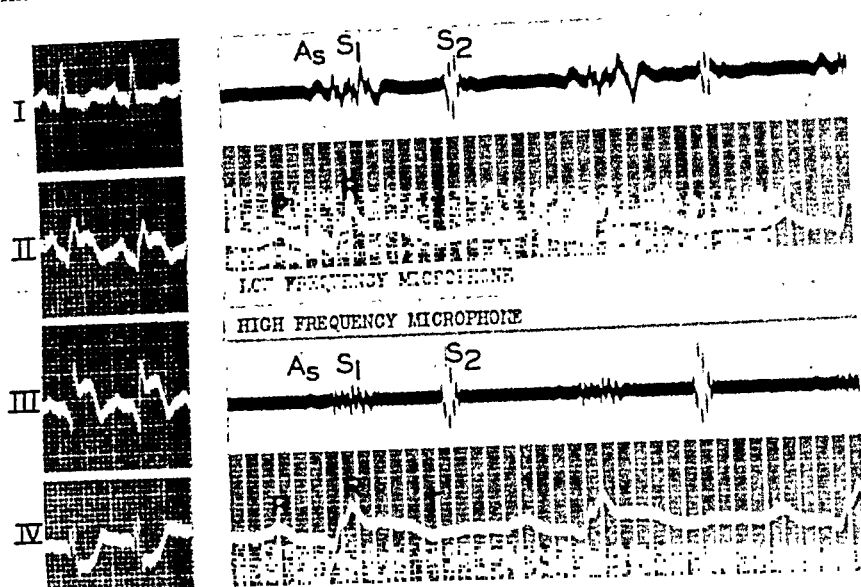


Fig. 2.—B. K. Male, aged 48. Acute coronary occlusion, fourth day. Electrocardiogram characteristic of acute posterior infarction (Q-T₁ pattern). Phonocardiogram reveals marked diminution in amplitude of the first sound (S₁) affecting particularly the central group of high-frequency vibrations. The second sound (S₂) is of high amplitude. A prominent low-pitched auricular sound (A_s) is present and was faintly audible.

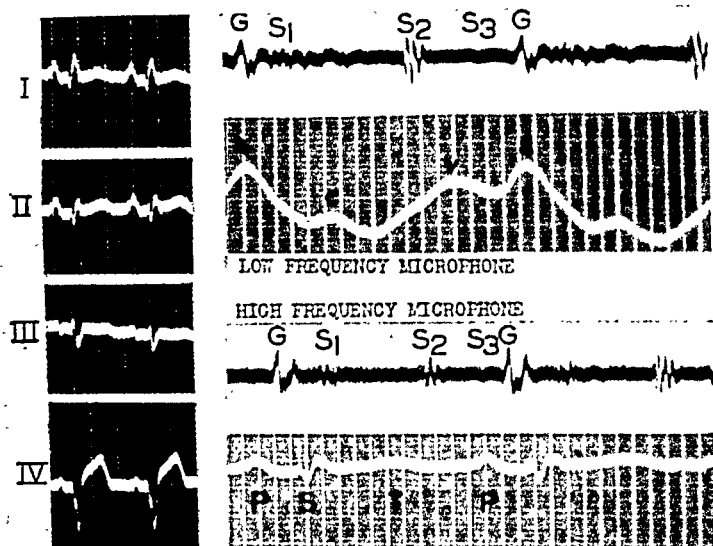


Fig. 3.—Male, aged 49. Coronary occlusion, sixth day, anterior infarction (Q₁-T₁₋₄). Phonocardiogram shows marked diminution of S₁ and presystolic gallop. The prominent gallop (G) is an accentuated auricular sound, corresponding to the "a" wave of the phlebogram. A faint low-pitched S₂ is visible.

to the ear; in addition, a good number of patients definitely gave the impression on auscultation that the second sound was actually louder than normally. In eleven cases we had definite phonocardiographic evi-

dence of this increase in amplitude of the second sound absolutely as well as relatively (Fig. 2). Parsonnet and Hyman³ also observed this. In Table III are listed the ratios of the amplitude of the first and second sounds in serial records of these patients. These cases were chosen because the amplification of the high frequency microphone was kept constant throughout the patient's illness (usually $6\frac{1}{2}$ to 8).

TABLE III

CONCOMITANT CHANGES IN AMPLITUDE OF FIRST AND SECOND SOUNDS IN CORONARY OCCLUSION

CASES	S ₁ TO S ₂ (MM.)	S ₁ TO S ₂ (MM.)
1	5 : 8	10 : $3\frac{1}{4}$
2	11 : $4\frac{1}{2}$	$3\frac{1}{2}$: 16
3	$6\frac{1}{2}$: 9	$5\frac{1}{4}$: $13\frac{1}{2}$
4	9 : 4	4 : 10
5	3 : 5	4 : $10\frac{1}{2}$
6	5 : 3	3 : 10
7	6 : $9\frac{1}{2}$	$4\frac{1}{2}$: 12
8	$11\frac{1}{2}$: 9	8 : 16
9	$4\frac{1}{2}$: 13	$11\frac{1}{2}$: 7
10	9 : 4	6 : 15
11	7 : 6	$3\frac{1}{2}$: 12

3. *Additional Heart Sounds:* (a) *Auricular Sound.*—An auricular sound was present in 83 per cent of the patients. In 50 per cent it was not significant since it showed the same configuration (1 to 2 vibrations of low frequency and amplitude) observed in 38 per cent of the normal phonocardiograms. The remaining 33 per cent of the auricular sounds in the coronary group were significant since they showed increased amplitude and formed a presystolic gallop. The latter is discussed later.

(b) *Third Sound.*—This sound was present in 47 per cent of the patients. It showed the normal configuration of the third heart sound found in 12 per cent of our control group, except for 9 per cent in which the amplitude was increased, giving rise to a protodiastolic gallop.

(c) *Gallop Rhythm.*—Working independently Wolferth and Margolies,²⁶ Battro, Braun Menendez and Orías,²⁷ and also Duchosal²⁸ arrived at the conclusion that the sounds forming gallop rhythm represented merely an exaggeration of phenomena normally present but often inaudible because of their low amplitude and frequency. Taking simultaneous phonocardiograms and phlebograms for the proper identification of the gallop sound and using the classification proposed by Wolferth and Margolies,²⁶ these authors showed that a presystolic gallop was produced by an auricular sound of increased amplitude and that a protodiastolic gallop represented an accentuated third sound. A summation gallop was formed by the superimposition of the auricular and third sounds of normal or accentuated amplitude, this fusion being complete or incomplete depending upon the heart rate. In our series a presystolic gallop occurred in 33 per cent of the patients (Table I) and was associated with heart failure in twenty-four of the twenty-six cases

(Table IV). It is of interest that each of the twenty-four cases had a first heart sound of diminished amplitude (Fig. 3). A protodiastolic gallop (Fig. 4) was found in only 9 per cent of the patients, and a summation gallop, in only 6 per cent, all of these also being associated with manifest heart failure.

TABLE IV

CORRELATION BETWEEN HEART FAILURE AND HEART SOUNDS IN CORONARY OCCLUSION

	NO. OF CASES	HEART FAILURE	
		PRESENT	ABSENT
$S_1 < S_2$	42	37 (88%)	5 (12%)
$S_1 = \text{or} > S_2$	36	12 (33%)	24 (67%)
Gallop rhythm	38	36 (95%)	2 (5%)

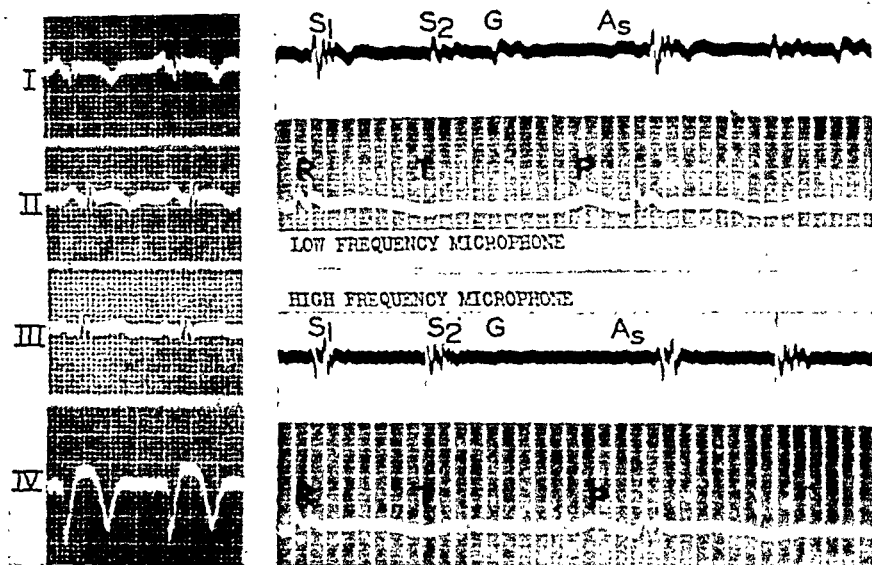


Fig. 4.—M. H. Male, aged 42. Acute coronary occlusion, fourth week. Electrocardiogram characteristic of recent anterior infarction (Q_{1-a-T_1} pattern). Phonocardiogram shows diminished amplitude and loss of high-pitched components of the first sound (S_1) and protodiastolic gallop rhythm (G) due to an accentuated third heart sound. A normal auricular sound (A_s) is also visible preceding S_2 . All these findings were present since the second day of the attack.

COMMENT

First Sound.—We have shown that changes in the character of the first heart sound usually occur immediately following an attack of acute coronary artery occlusion and persist throughout the illness. The use of low-frequency and high-frequency microphones revealed diminution in amplitude of the central group of vibrations which normally are of very high amplitude and frequency and which occur during the isometric contraction phase of the ventricles.

This change in the first sound is audible as a "dull, muffled" or "poor" sound. Since the number of vibrations, the duration, and average frequency of the first sound did not show any significant change

from normal, the explanation of the peculiar change in pitch of the first sound must be sought in the diminution in amplitude of the central group and in the so-called masking effect.²⁹ The latter implies that a low-pitched sound of great intensity "masks" a sound of higher pitch which is not too distant from it in the frequency scale but of comparatively lesser intensity. Thus, the masking of the faint high-frequency components of the first sound by the relatively prominent low-frequency elements produces the auscultatory impression of a dull, muffled or poor first heart sound in coronary occlusion. However, in the phonocardiogram recorded with a proper filtering and amplifying system, all the frequencies, while diminished in amplitude, are present in a number not differing from the normal.

It seemed logical to consider the loss of amplitude of the first sound the result of lowered intraventricular pressure resulting from the impaired contractility of the infarcted ventricular muscle. Perhaps this is a factor in the first few days or more, when the patient is acutely ill, the cardiac output diminished, and the blood pressure low. However, this explanation does not account for the persistence of the low first sound after the patient has recovered from the initial phase of the attack, and often for months and years later when the patient's condition may be good, without heart failure, and with normal blood pressure and cardiac output. Hence one must assume that some change in the physical properties of the damaged left ventricle is the cause of the diminution in amplitude of the central group of vibrations of the first heart sound.

The great majority of patients (37 of 42) with this type of diminished first sound showed signs of heart failure while those with an unimpaired first heart sound developed none or only a very mild and transient degree (Table IV).

The change in the character of the first sound in coronary occlusion is of diagnostic importance. We have seen that it is present in 79 per cent of patients during the acute and subacute phases and a follow-up study of patients who have recovered from coronary occlusion reveals a tendency for it to persist for years. Only a limited number of follow-up patients have been studied phonocardiographically, but in a clinical investigation³⁰ of 202 cases followed for an average period of three years after the acute attack it was found that the first sound remained of abnormally low pitch and intensity in half the cases. An impaired first sound may be the only sign remaining after an acute attack of coronary occlusion, and, whenever it is found in a person of the coronary age group, the possibility of a previous attack of acute coronary occlusion should be borne in mind.

Second Heart Sound.—The explanation of the absolute increase in the second heart sound which occurs not infrequently in coronary occlusion is not clear. It is accepted that the second heart sound is produced by

heart failure in coronary occlusion⁴ accounts for the high incidence of gallop rhythm (47 per cent).

The close association of gallop rhythm with heart failure was apparent in our series in which all but two of thirty-eight patients presenting gallop rhythm had heart failure (Table IV). Any of the three types of gallop rhythm may be associated with heart failure, but the presystolic type is most frequently found. The cause probably is the increased intra-auricular pressure present in heart failure. The high incidence of gallop sounds in coronary occlusion cannot be regarded as specific since true gallop rhythm is also found in heart failure due to hypertensive or rheumatic heart disease. However, the association of gallop rhythm and impaired first heart sound in coronary occlusion deserves particular emphasis since it is rarely encountered in heart failure due to other causes.

SUMMARY

A phonocardiographic analysis employing microphones of different frequency filtering and transmission range was made of the heart sounds in seventy-eight cases of acute coronary occlusion and in 100 normal control subjects. The results were correlated with the clinical findings.

The first heart sound was absolutely diminished in amplitude in 24 per cent and relatively to the second sound in 54 per cent of the patients with acute coronary occlusion. This diminution in amplitude affected the central group of high-frequency vibrations and was attributed to the change in the physical character of the infarcted left ventricle and possibly, in the first few days of illness, to the lowered intraventricular pressure following acute myocardial infarction.

Occasionally the second sound at the apex is increased to an absolute as well as a relative value.

An auricular sound was present in 83 per cent of cases of coronary occlusion compared to 38 per cent in normal subjects. In one-third of the cases of coronary occlusion the auricular sound was accentuated and formed presystolic gallop rhythm. This never occurred in normal subjects. Accentuation of the auricular sound was probably the result of the increased intra-auricular pressure following ventricular infarction. It was practically always associated with heart failure.

A third sound occurred in 47 per cent of the cases of coronary occlusion as compared to 12 per cent in normal subjects. The high incidence in the former was attributed to the decreased tonus of the infarcted ventricular muscle. In 9 per cent of the cases the third sound appeared accentuated and produced protodiastolic gallop rhythm. Heart failure was invariably associated with it.

Superimposition of the auricular and third sounds of normal or accentuated amplitude occurred in 6 per cent of cases, forming summation gallop. This type of gallop rhythm was also associated with heart failure.

Clinical heart failure was present in 63 per cent of the cases of coronary occlusion. It occurred predominantly in those who presented a first sound of diminished amplitude (88 per cent) and gallop rhythm (95 per cent). It was much less common in those with an unimpaired first sound (33 per cent). This emphasizes not only the close relationship between impaired heart sounds and heart failure but also the serious import of a diminished first heart sound and gallop rhythm.

Gallop rhythm may be present before signs of heart failure are apparent.

The impairment of the first heart sound following coronary occlusion is often permanent and may be the only persistent sign following recovery. It thus may be of diagnostic significance.

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SPONTANEOUS CHANGES IN THE NORMAL RABBIT ELECTROCARDIOGRAM

HAROLD D. LEVINE, M.D.
BRISTOL, N. H.

AS A COROLLARY to another research, it was necessary to make a control study of the spontaneous day-to-day variations in the normal rabbit electrocardiogram. Although similar controls may have been made in the course of other electrocardiographic investigations on rabbits, they must be considered as buried, as it were, and hence unavailable as a standard for future reference. A careful search of the literature, moreover, revealed no publication dealing purely with the normal rabbit electrocardiogram. In order, therefore, to avoid further unnecessary and uneconomical duplication of effort, and because the present research did show considerable spontaneous variation in the appearance of the tracings, awareness of which might keep the investigator in this field from going astray, presentation of these observations is considered desirable.

METHOD

In these experiments, five-lead electrocardiograms were taken on every second, third, or fourth day with a vacuum-tube type of electrocardiograph (Cardiette). The skin was first clipped or shaved over an area about the size of an ordinary surface electrode on the left and right forelegs and the left hind leg close to the trunk, and over the anterior surface of the chest. In a few instances mercuric sulfide was used as a depilatory, and this saved a good deal of time. The bare areas were then rubbed with Redux electrode paste, and the surface electrodes were applied and kept in position with elastic bands. In addition, chest leads were taken by applying an electrode to the chest wall and attaching it to the left leg cable; this was coupled with the left arm cable, attached to the left leg electrode. The tracings were then taken with the lead switch on Lead III. Two chest leads were taken, one from the left and the other from the right side of the anterior surface of the thorax. In both cases the cephalic end of the electrode impinged exactly in the apex of the axilla and the median side of the electrode was exactly in the midline of the sternum. The animal was allowed to assume a natural prone position, and, after initial evidences of fear had subsided, and it was made certain that there was no rotation of the thorax about its longitudinal or transverse axis, the tracings were taken. The use of restraint was avoided as far as possible. In a few cases, fright could be overcome by putting a loose towel over the animal's head. The records were carefully standardized so that 1 millivolt produced a deflection of 1 cm.

Because of the looseness of the skin over the rabbit's chest, it was difficult to be sure that exactly the same relationship held between the position of the electrode and the position of the heart at different times. Nor would this difficulty be obviated by the use of needle electrodes. However, in several instances the chest leads were re-

Received for publication Jan. 7, 1942.

peated after removing and reapplying the chest electrodes, and identical tracings were obtained. By removing and deliberately reapplying the chest electrode 1.5 cm. mesiad, laterad, cephalad, or caudad to its original application, marked differences in the appearance of the tracing were produced. Such changes could easily be produced by inadvertently sliding the skin over the thorax in applying the chest electrodes. The appearance of the conventional limb leads, by contrast, is very little if at all affected by slight differences in the application of the electrode to the limb. Accordingly, it is felt that greater importance must be attached to spontaneous changes in the conventional leads than in the chest leads.

On nine normal male rabbits, ranging in weight from 1.5 to 3.0 kg., five-lead electrocardiograms were taken at intervals of one to four days for a period of two weeks; on the average, one series of tracings was taken every other day. Also included in this study are the initial control tracings from a series of fourteen animals that subsequently formed part of another investigation.¹ Thus multiple observations are available on nine, and single observations on fourteen, rabbits, making a total of twenty-three animals. A total of 335 records was obtained on these twenty-three rabbits. As far as possible, the tracings were made at about the same time of day and at about the same time after eating. A comparator was used to measure the height of the various components of the tracings. When the height of an individual wave varied from complex to complex, as it frequently did, the average of several measurements was recorded. Daily recordings were made of the rectal temperature. The nine animals on which repeated electrocardiograms were made were sacrificed after the final electrocardiograms, and numerous microscopic sections were made of the heart. In no case were pathologic changes found.

RESULTS

Static Considerations.—The results are best expressed in the form of a composite tabulation giving the minimum and maximum, as well as the median and mode, of all the measurements made on the twenty-three animals (Table I). It should be noted that just as many observations exceed as are exceeded by the *median* value in height or duration. The *mode*, on the other hand, is the measurement most frequently made. In this discussion Lead L refers to the derivation from the left anterior chest, and Lead R, to that obtained from the right anterior chest.

The P wave, when measurable, was usually upright, but occasionally inverted, in Leads I and L. It was occasionally inverted, but usually upright, in Lead III. It was always upright in Lead II. In Lead R, the P wave was usually inverted, occasionally diphasic, but never purely upright.

The P-R interval varied from 0.06 to 0.09 in Lead I, from 0.06 to 0.10 in Leads II and III, and from 0.06 to 0.08 in the chest leads (L and R), but the median and mode for all leads was 0.07 second. A Q wave was more often present than absent in Leads I and L. It was generally absent in the other leads, but depths of 1.6 to 6.5 mm. were recorded occasionally. Very frequently there was no R wave in Lead I; this wave was generally well developed in all the other leads, especially Lead II. The S wave, too, was, more often than not, absent in Lead L. It was occasionally present in Lead II, and usually well marked in Leads III and R. It was present in about half the tracings in Lead L.

was reversal in the direction of the major deflection of the QRS complex. In Fig. 1, for example, the major QRS₁ deflection is downward in the first (Sept. 22, 1941) and last (Oct. 4, 1941) tracings, but upright in the intervening ones. Similarly, in Fig. 2, although the exploring electrode was applied identically at all times, the major QRS deflection in the left chest lead was upright in the first (Sept. 22, 1941), fourth (Sept. 27, 1941), and fifth (Oct. 1, 1941) tracings, but downward in the second (Sept. 24, 1941) and third (Sept. 26, 1941). Changes in the voltage and form of the T wave were much more striking and frequent. In Fig. 1, T₁ is sharp and measures 2.4 mm. in height (Sept. 22, 1941).

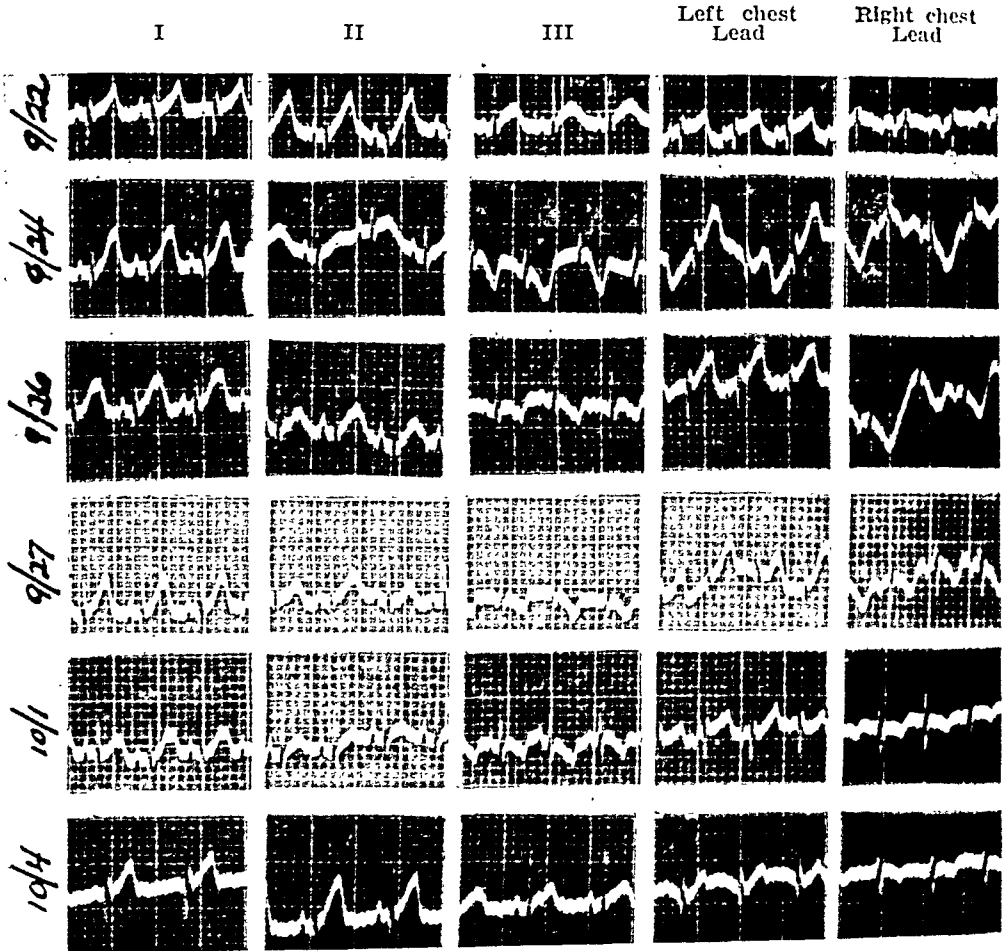


Fig. 1.—Serial, five-lead electrocardiograms from rabbit, showing (1) spontaneous variations in the voltage of the QRS complex, (2) spontaneous inversion of T₁, with subsequent return to upright position, (3) change in the contour of T₁ from sharp to rounded, with subsequent return to sharp outline, and (4) persistent, slight elevation of RS-T in Lead L.

On the next occasion it was more rounded and measured 4.1 mm. in height. Spontaneous reversal in the direction of the T wave in all leads, except Lead II, is another feature of the normal rabbit electrocardiogram. This was recorded only once in Lead I, but, in over half the cases in which repeated electrocardiograms were taken, there was spontaneous T₂ inversion, with subsequent return to the upright direction.

T_1 , although generally upright, likewise frequently showed variation in voltage and occasionally reversal of direction. T in Lead R was generally inverted, but in two cases it was upright for a time. These variations are well illustrated in Figs. 1 and 2. In the former, slight deviations of the RS-T segment are also shown. Such deviations never exceeded 1 mm.

Although the P-R interval showed spontaneous variations of 0.01 to 0.02 second, its total duration never exceeded 0.10 second in the conventional limb leads or 0.08 second in the chest leads. In several instances there was spontaneous lengthening of the P-R interval from 0.07 to 0.08 or 0.09 second, without change in the heart rate. In the few cases in which the P-R interval was 0.10 second, there was an associated slowing of the heart. The duration of the QRS complex was invariable (0.03 second).

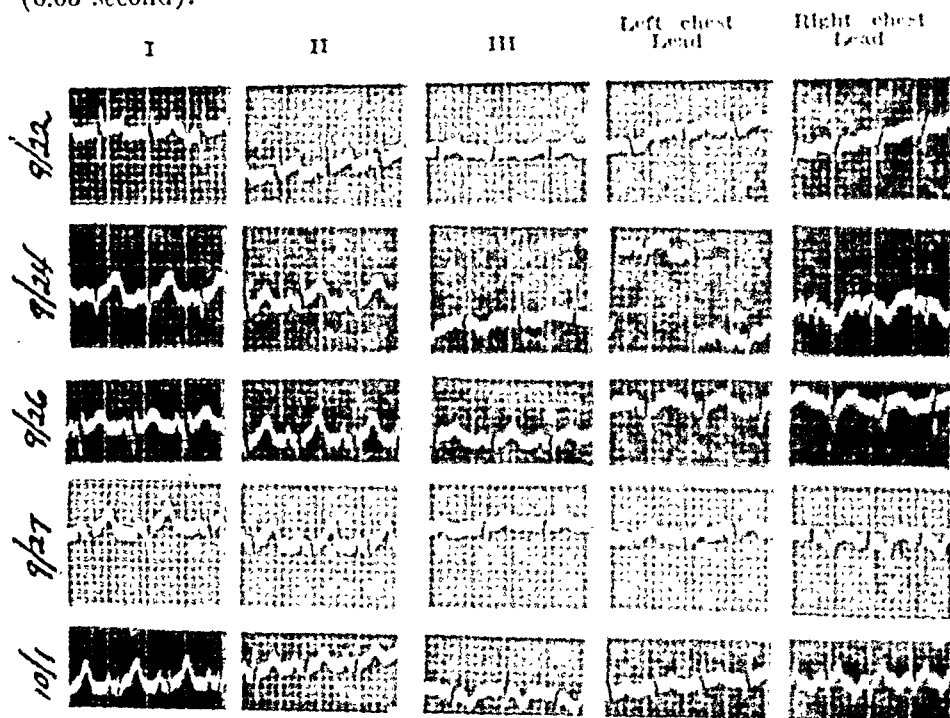


Fig. 2.—Serial, five-lead electrocardiogram from rabbit, showing (1) spontaneous variations in the voltage of the P wave, QRS complex, and T wave, (2) spontaneous inversion of T_1 at second and fifth recordings, (3) spontaneous reversal of T in Lead R from inverted to upright direction at third recording, with subsequent return to inversion, and (4) transient, slight elevation of RS-Ts.

There were no instances of transient or permanent extrasystoles, auricular fibrillation or flutter, auricular or ventricular tachycardia, intra-ventricular block, bundle branch block, or auriculoventricular heart block in this series of observations. Tracings from a struggling, restrained animal, preceding and during the infusion of a solution into the ear vein, did show frequent ventricular extrasystoles, with bigeminal and trigeminal rhythm, but, as stated above, such changes were not observed in the unrestrained animal.

COMMENT

Vizer and Haban² noted the variability of the rabbit electrocardiogram from animal to animal, but they did not describe serial changes in individual animals. The present observations are in accord with those of Becke, Johnson, and Harris,³ who, likewise, found no major disturbances in the conduction mechanism, but these investigators failed to find T-wave changes in their control animals, and attached considerable importance to changes in the T waves which became diphasic or inverted. It emerges from the present study, however, that similar importance can be attributed to such changes only if they are present in Lead II, for they may occur spontaneously in any of the other leads.

Such changes as have been recorded may be due to variations in the vagus mechanism,⁴ to extreme mobility of the rabbit's heart, producing unavoidable changes in the position and hence of the electrical axis of the heart (such as Katz, Soskin, and Frisch⁵ have assumed is the case in the dog's heart), or to intrinsic electrochemical changes in the heart itself. It is the purpose of this report merely to record the fact that there are such changes, not to establish their mechanism.

SUMMARY

The rabbit electrocardiogram exhibits marked spontaneous changes in the form, voltage, and direction of many of its components. Transient reversal of the T wave in Leads I and II and in the chest leads is frequently observed. T₂ is constantly upright. Slight RS-T segment deviations, never exceeding 1 mm., are frequently encountered. The P-R interval never exceeds 0.10, and the duration of the QRS complex never exceeds 0.04, second. Abnormal rhythms are not seen in the normal, unrestrained, unanesthetized rabbit.

Cognizance of these spontaneous changes in the rabbit electrocardiogram is essential to the intelligent appraisal of experimental studies on the rabbit heart.

My sincerest thanks are due John H. Westfall, V.S., for his assistance in carrying out these experiments.

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AURICULAR FIBRILLATION OF LONG DURATION IN RHEUMATIC HEART DISEASE

CHARLES E. KOSSMANN, M.D., AND CHARLES A. R. CONNOR, M.D.
NEW YORK, N. Y.

AURICULAR fibrillation is generally regarded as a terminal event in the course of rheumatic heart disease. The permanent establishment of this arrhythmia after the age of 30 years in a person with rheumatic heart disease is a grave prognostic omen, as the mean duration of life is two years^{1, 2}; the prognosis is even more grave when auricular fibrillation begins before the age of 20, as the mean duration of life is then less than one year.¹⁻³ The life expectancy curve of adults with rheumatic heart disease and auricular fibrillation is positively skewed¹; that is, it shows that only 25 per cent will live three years or longer after the onset of the arrhythmia. A few live as long as ten years.

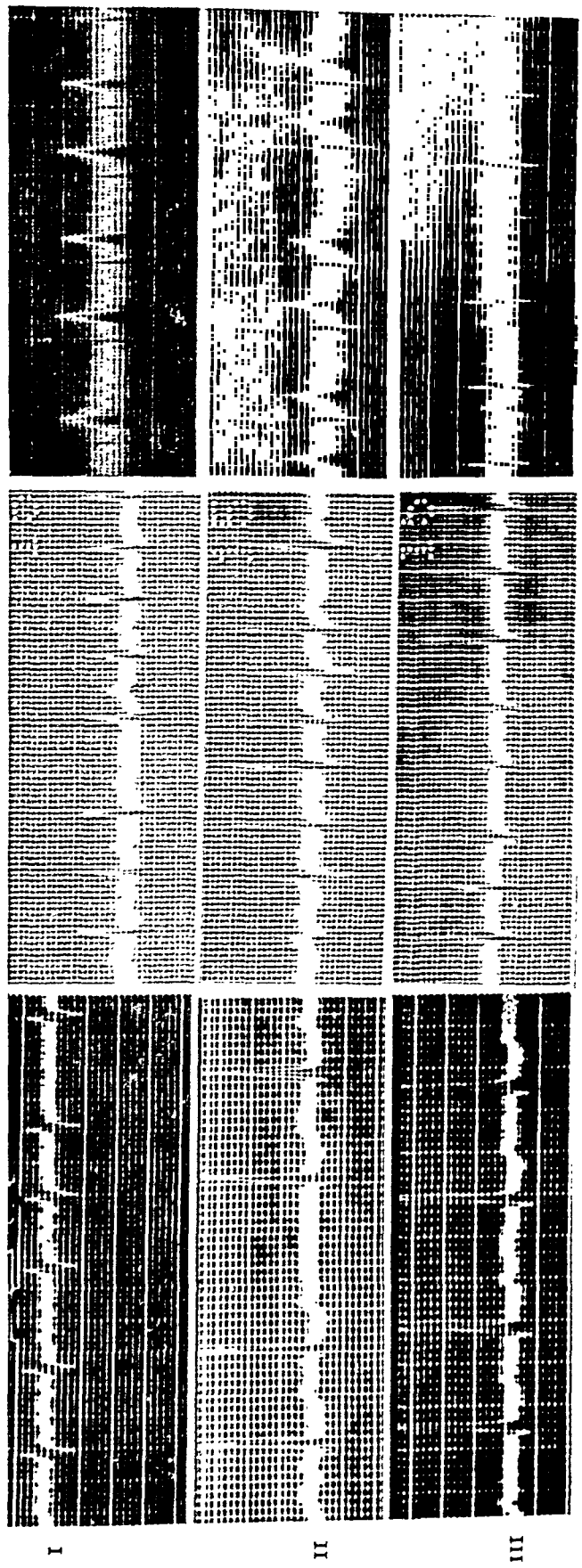
In a group of 276 adults with rheumatic heart disease and auricular fibrillation studied by DeGraff and Lingg,¹ the longest period a patient lived was twelve years. Levine⁴ observed a case of this kind for seventeen years. Bishop and Bishop⁵ have reported a patient with auricular fibrillation of twenty-five years' duration. The onset occurred at the age of 55 years. Necropsy revealed atherostenosis of the left coronary artery, in addition to rheumatic mitral stenosis. It is likely that arteriosclerosis was the etiologic factor in this instance rather than rheumatic infection because of the onset of the arrhythmia at a rather advanced age.

The three cases herein reported were unusual in that each had mitral stenosis of rheumatic origin with auricular fibrillation of fourteen, sixteen, and twenty-one years' duration, respectively. The abnormal rhythm began in each subject at an early age, and death occurred at 57 years, 33 years, and 45 years (Table I). This fact combined with other clinical data, and the pathologic findings observed in one of these patients make it likely that rheumatic fever was the only etiology involved in all three instances.

CASE 1.—S. A., a white male, was told he had heart disease when he was 15 years old. At 23 he had "rheumatism" of both ankles for one month. About the same time he noted a soft penile sore. No further details of this lesion are available. On July 10, 1914, during his twenty-fourth year, he was admitted to Bellevue Hospital in congestive heart failure. In the next four years he was admitted six

From the Department of Medicine, New York University College of Medicine, and the Cardiac Clinic of the Third (New York University) Medical Division, Bellevue Hospital.

Received for publication Dec. 26, 1941.



A. *B.* *C.*
Fig. 1.—*A*, S. A., Nov. 19, 1915. *B*, J. A., March 24, 1922. *C*, S. Y., April 13, 1925.

additional times, with the same syndrome, for an average stay of five weeks each time. With bed rest and digitalis he would improve, only to lapse into failure shortly after resumption of moderate physical activity. Of interest was the occurrence of hoarseness during the first nine months of observation.

On each admission between 1914 and 1918 the heart was enlarged. Presystolic and systolic thrills were felt, and corresponding murmurs were heard, at the apex. On occasions a systolic murmur, a diastolic murmur, or both, were heard in the aortic area; at other times neither one was audible. Two observers noted a systolic murmur in the tricuspid area, and one of these heard a diastolic murmur as well in 1915. The pulmonic second sound was always louder than the aortic second. The pulse was rapid, irregular in rate and force, and small. The ventricular rate, without the benefit of digitalis, varied from 100 to 180 beats per minute with a pulse deficit of 25 and 60 beats. The blood pressure range was from 110/70 to 170/100.

Other physical findings were those of congestion; i. e., distended veins of the neck, râles at the bases of the lungs, large tender liver, and edema of the ankles. Fluid was noted in the right side of the chest and was removed in amounts from 480 c.c. to 1,200 c.c. on four different occasions between 1914 and 1916. A fluid wave in the abdomen was always equivocal.

Evidence of rheumatic activity, other than heart failure and auricular fibrillation, was usually scanty.⁶ The first few days of each admission the temperature was approximately 101° F., but soon fell below 99.6° F., and with a few brief exceptions remained there until his discharge. Leucocyte counts on admission were also slightly elevated. The blood Wassermann reaction was positive (12 to 15 units) in 1914, but thereafter was negative. Iodides orally and twenty intramuscular injections of mercury salicylate were the only antisyphilitic therapy given.

The first electrocardiogram was recorded on Nov 9, 1915. It displayed auricular fibrillation with a low T_1 and a diphasic T_2 and T_3 , and right axis deviation (Fig. 1A). Subsequent electrocardiograms showed no significant changes.

From April, 1918, to April, 1923, the patient attended the clinic irregularly but took digitalis most of the time. He was regarded as having rheumatic heart disease with mitral stenosis and insufficiency complicated by auricular fibrillation. Functional tricuspid insufficiency was thought to have existed during his bouts of failure.

From 1923 to 1934 his case was not followed. In February of the latter year he was readmitted to the hospital because of increasing weakness, dyspnea and orthopnea of one month's duration, all of these symptoms having followed an upper respiratory infection. In the interim of eleven years he had been working steadily as a shipping clerk and had taken digitalis during the winter months only. On several occasions he had slight ankle edema, but only once (in March, 1933) was it severe enough to cause complete bed rest.

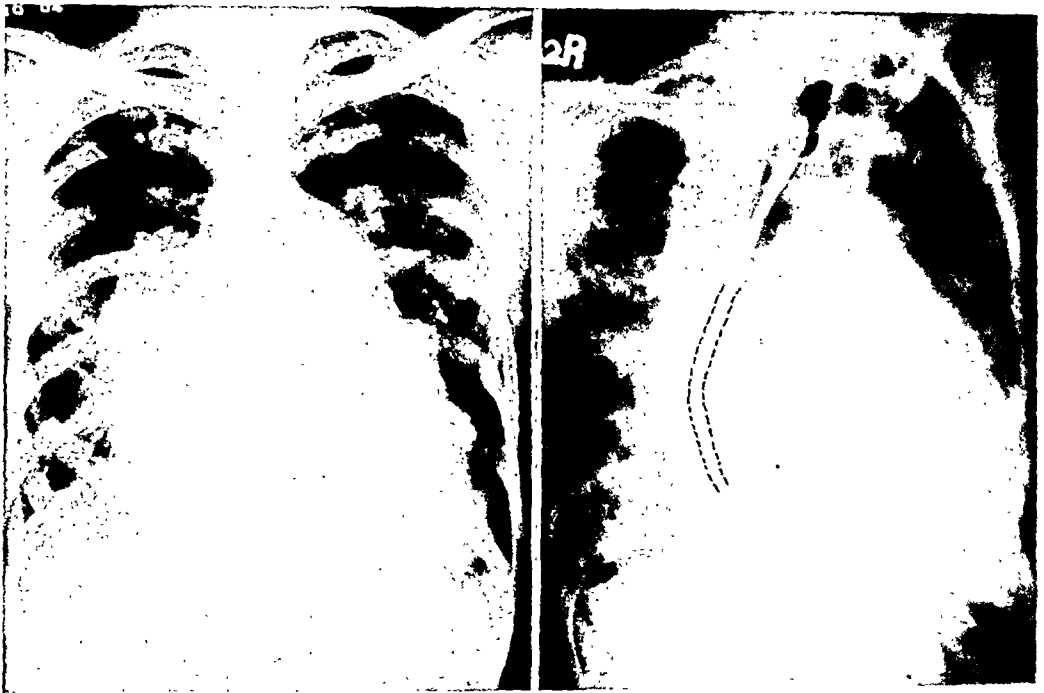
The only new physical finding was a paralyzed left vocal cord.⁷ Hoarseness had been present for a year. The ventricular rate was 80 beats per minute although digitalis had not been taken regularly. The only evidence of rheumatic activity was a slight increase in the leucocyte count and a rapid sedimentation of the erythrocytes. A teleroentgenogram of the chest (Fig. 2A) revealed an unusual cardiac silhouette, characterized by prominent bulges on both sides, somewhat higher on the right, which was interpreted as a greatly enlarged left auricle. An esophlogram (Fig. 2B) showed considerable posterior displacement of the esophagus by the left auricle.

The patient quickly improved on rest in bed and digitalis. From March, 1934, to Oct. 24, 1935, he was ambulatory on whole leaf digitalis, 0.2 Gm. daily. On his last visit to the clinic on the latter date he complained of increasing dyspnea, vague pains in the abdomen, and anorexia. Vomiting began on November 9.

The patient entered the hospital for the ninth and last time on November 14. He was acutely ill. Abdominal distention and rigidity were marked. Blood was discovered in the vomitus and in the stool. The temperature was 101° F., and there was no leucocytosis. Heart failure was not marked. His course was rapidly downhill, and he died Nov. 18, 1935, at the age of 45 years, of what was thought to be a mesenteric thrombosis with infarction of the intestine.

Necropsy.—Only the important pathologic changes are noted.

Heart (Gross Examination).—The weight was 700 Gm. There was extreme dilatation of the left auricle with atrophy of myocardium and marked endocardial sclerosis. Epicardial fibrosis of the left auricle was present. Organizing thrombi were found in both auricular appendages. Marked hypertrophy and replacement fibrosis of the right auricular myocardium and old infarction of the right crista terminales were evident.



A.

B.

Fig. 2.—A, S. A., April 16, 1934. B, S. A., Feb. 27, 1934.

Heart (Histological Examination).—There were healed mitral valvulitis (rheumatic type) with calcification and stenosis, healed tricuspid valvulitis or persistent vascularization of the leaflet, persistent vascularization of the pulmonic valve, aortic valvular sclerosis or healed valvulitis, and diffuse perivascular and moderate interstitial replacement fibrosis of the ventricles.

Aorta.—Atherosclerosis was evident in the aorta.

Lungs.—Obliterative pleuritis was seen in the right lung. Both lungs showed emphysema, congestion, pulmonary atherosclerosis, and moderate anthracosis.

Liver.—Cardiac cirrhosis with fatty change was noted.

Spleen.—Chronic passive congestion and arteriolar sclerosis were present in the spleen.

Gastrointestinal Tract.—There were hemorrhagic infarction of the ileum (gangrene), submucosal hemorrhages of the stomach, congestion of the small intestine, and acute serofibrinous peritonitis.

Kidneys.—Arteriolar nephrosclerosis, multiple healed infarcts, and congestion were observed.

It is to be noted that no evidence of rheumatic activity was found and that no occlusive disease was discovered in the abdominal cavity to account for the gangrenous ileum. A potential source of emboli, however, was found in both auricular appendages.

CASE 2.—J. A., a white female, had frequent sore throats since the age of 3, and pains in the muscles and joints, especially in the winter and spring, since the age of 7. She never had a typical attack of polyarthritis or chorea.

At 9 years she experienced dyspnea on effort accompanied by orthopnea, cough, and palpitation. The diminution of her cardiac reserve progressed in the next two years to cardiac failure, for which she entered another hospital at the age of 11 years. An enlarged heart and evidence of mitral stenosis and insufficiency were discovered at this time, but no notation was made of an arrhythmia. After two months of complete rest in bed, she was discharged improved.

Between the ages of 11 and 16 years she was free from symptoms of heart failure but continued to have frequent sore throats and pains in the muscles. The second episode of heart failure occurred in December, 1921, at the age of 16, at which time she was first admitted to Bellevue Hospital. Auricular fibrillation was noted then and at all subsequent examinations. The heart was enlarged, and there was clinical evidence of stenosis and insufficiency of the mitral valve. Digitalis was begun at this time, and she was discharged in March, 1922, improved.

The first electrocardiogram was recorded in the cardiac clinic on March 24, 1922. It showed auricular fibrillation with a ventricular rate of 140 per minute. There were no other abnormalities (Fig. 1B). Repeated electrocardiograms in subsequent years were similar.

She attended the clinic regularly for the next eleven years with little change in her cardiac status. In this period she took 0.2 Gm. whole leaf digitalis daily. There were no definite signs of rheumatic activity other than the fact that she developed aortic insufficiency in 1928. Her functional capacity remained good.

She had completed college and was working in 1932 when she began to develop fatigue, dyspnea, orthopnea, and cough. As these symptoms increased, despite extra rest at home, she was readmitted to the hospital on March 29, 1933, in severe congestive heart failure. There were basal pulmonary râles on admission, and later she developed a moderate effusion in the right pleural cavity. The liver was greatly enlarged. There was massive edema of the lower extremities. Her blood pressure on admission was 170/80; it fell to 135/80 on discharge. Her course was febrile; the leucocyte count was high; the erythrocyte sedimentation rate was elevated. A cardiac roentgenogram showed tremendous enlargement involving all of the chambers. During the remainder of her life she always displayed a similar cardiac silhouette. After nine months of bed rest, digitalis, and diuretics, she improved somewhat and was discharged to the clinic in December, 1933, on a maintenance dose of 0.3 Gm. of whole leaf digitalis daily.

From this time on her cardiac reserve was greatly diminished, and she spent a large part of each day in bed. She was admitted to the hospital in January, 1935, for an alveolar abscess, and again in August of the same year for a recurrence of pains in the joints, but on neither of these occasions was the cardiac status much changed. The same was true of her course in the clinic during the next two years.

On the evening of Dec. 29, 1937, after a hearty meal, the patient died suddenly while preparing to retire. She was 33 years old. No necropsy was obtained.

CASE 3.—S. Y., a white female schoolteacher, had severe growing pains between the ages of 9 and 12, and an attack of chorea at 12 years, which lasted for several

months. At 15 years a heart murmur was discovered, but, as she had no symptoms, her physical activity was not curtailed.

In 1910, at the age of 29, she was first seen by Dr. Joseph H. Bainton and remained under his care until 1935. His records reveal that there were no cardiac symptoms in 1910. There were a presystolic thrill and murmur limited to the apical region, but no enlargement of the heart. The second aortic and pulmonic sounds were of good quality and of equal intensity. The rhythm was regular; the rate was 68 per minute; and the blood pressure was 105/84.

The following year she had mild articular pains on several occasions, usually associated with or immediately following an upper respiratory infection. Palpitation on effort was initially noted at this time, but the pulse was always regular. The patient was digitalized, but the drug was discontinued when it proved ineffectual for this symptom.

In 1916, at the age of 35, a blood-streaked sputum was produced on several occasions. In 1917 a severe attack of follicular tonsillitis occurred and was followed by mild pains in the joints which persisted for several months. During this time there was no fever.

In the period from 1917 to February, 1923, there were no joint pains, although occasionally she complained of palpitation and had hemoptysis on a few occasions. In 1923 the patient had a prolonged period of hemoptysis accompanied by pain in the precordial area. This episode was considered a left lower lobe pulmonary infarct. Immediately after this episode, she developed signs and symptoms of heart failure.

Physical examination at this time revealed no change in the cardiac findings, except that the rhythm was irregular due to many premature contractions, the exact origin of which was not determined. There were moist râles at both lung bases, but no other objective findings of congestive heart failure. Digitalis was again administered, this time with success, and she was kept on a daily maintenance dose of 0.1 Gm. whole leaf digitalis.

During an attack of acute bronchitis in February, 1924, at the age of 43, auricular fibrillation, proved by an electrocardiogram (Fig. 1C) began and persisted for the remainder of her life. Except for the arrhythmia, the electrocardiogram showed no other alteration from the normal. No signs of heart failure developed with this change in rhythm, presumably because she was fully digitalized. Her blood pressure was normal.

Three months after the onset of auricular fibrillation, an embolus lodged in the right popliteal artery, but recovery was rapid. Nothing of importance occurred until January, 1928, four years after the onset of auricular fibrillation, when another embolus lodged in the left popliteal artery, but again adequate collateral circulation developed and there was no residual vascular insufficiency.

Late in 1930, the patient's cardiac reserve began to decrease considerably. An orthodiagram at this time showed a moderately enlarged heart, the actual transverse diameter being 14 cm., while the predicted diameter, based on the Hodges-Eyster formulas, was 11.3 cm. The left auricle was seen to be enlarged in the lateral and oblique views. The heart continued to increase in size, and on the last orthodiagram in 1936 the transverse diameter measured 15.7 cm. In November, 1930, she developed classical signs of infarction of the lower lobe of the left lung. From then until 1935, she had moderate dyspnea on effort, and during most of the time râles were heard at both pulmonary bases. During this interval the blood pressure rose steadily to hypertensive levels, so that by the end of 1935 the systolic pressure was over 200, and the diastolic, over 100 mm. of mercury.

From 1935 to the time of her death, the patient was under the care of Dr. Clarence E. de la Chapelle and one of us. In 1937 she took a sabbatical leave from her teaching duties for the first time. In October of that year, severe congestive heart failure developed after unusual physical exertion. This responded partially to rest in bed and ammonium chloride, so that she was able to be up and about the house. On the day of her death, Feb. 1, 1938, she awoke feeling well and made a visit to the school at which she taught. Upon leaving the school and while walking to a bus, she suddenly became dyspneic and cyanotic. She was taken home by taxicab, and died a few minutes after arriving. She was not seen by a physician immediately before death, and no necropsy was performed. It was surmised that a pulmonary embolus was the cause of death.

TABLE I
SUMMARY OF CASES

	CASE 1 (S. A.)		CASE 2 (J. A.)		CASE 3 (S. Y.)	
	YEAR	AGE IN YEARS	YEAR	AGE IN YEARS	YEAR	AGE IN YEARS
First rheumatic manifestation	1913	23	1912	7	1890	9
Discovery of cardiac disease	1905	15	1914	9	1896	15
First diminution of cardiac reserve	1914	24	1914	9	1911	30
Onset or discovery of auricular fibrillation	1914	24	1921	17	1924	43
First episode of congestive heart failure	1914	24	1916	11	1923	42
Subsequent failures	1914-18* 1933 1934	24-28 43 44	1921 1933	17 29	 1937	 56
Death	1935	45	1937	33	1938	57
Cause of death	Hemorrhagic infarction of the ileum		Unknown (sudden)		Unknown (sudden)	
Duration of life after discovery of auricular fibrillation	21 years		16 years		14 years	
Years of employment after discovery of auricular fibrillation (cardiac reserve good)	15 years		12 years		13 years	
Final cardiac diagnosis†	(a) Rheumatic inactive. (b) Enlarged heart with massive left auricular hypertrophy and dilatation, mitral stenosis, mitral insufficiency. (c) Auricular fibrillation (d) III D		(a) Rheumatic inactive. (b) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency. (c) Auricular fibrillation (d) III D		(a) Rheumatic inactive, Hypertension. (b) Enlarged heart, mitral stenosis, mitral insufficiency. (c) Auricular fibrillation (d) III D	

*In chronic heart failure with remissions for the four-year period indicated.
†In accordance with *The Nomenclature and Criteria for the Diagnosis of Diseases of the Heart*, ed. 4.

of the Heart, ed. 4.

SUMMARY AND CONCLUSIONS

Three cases of rheumatic mitral stenosis complicated by auricular fibrillation were observed for periods of fourteen, sixteen, and twenty-one years, respectively. While under observation, one patient developed aortic insufficiency, and another, hypertension.

Although congestive heart failure contributed to the death of each, it was not the primary cause. In one, death was caused by gangrene of the ileum, although a mesenteric thrombus or embolus could not be demonstrated at necropsy. In the remaining two, death was sudden, suggesting an embolic accident. One case had four embolic accidents during life, two to the lungs and two to the lower extremities, exclusive of the final episode. The other two cases had no clinical evidence of embolization, except terminally.

All three had long periods, twelve, thirteen, and fifteen years, respectively, during which they were gainfully employed despite their auricular fibrillation. Two of them were constantly under the influence of digitalis, while in the other case this drug was taken irregularly.

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AURICULAR AND VENTRICULAR PERICARDIAL FRICTIONS

P. COSSIO, M.D., I. BERCONSKY, M.D., AND R. G. DAMBROSI, M.D.
BUENOS AIRES, ARGENTINA

A STUDY of heart sounds and murmurs was made by means of graphical registration excluding the pericardial frictions (Cossio,¹ Leblanc,² Orías and Braun Menendez,³ Caló,⁴ Pazzanese⁵). In one case (Caló⁴) there is a questionable record of pericardial frictions because of the time and low frequency of the vibrations, since the auscultation was negative and necropsy showed adhesive pericarditis. In the consulted bibliography another doubtful record of pericardial frictions was found (Dassen and Vitale⁶) and was due to the absence of well-differentiated vibration within a defective base line.

Two conditions may have caused the failure of graphical registration of pericardial frictions: (1) the rarity and (2) the incapacity of the devices in use.

There is no doubt that the second condition is the more essential in the failure of registration for other phenomena of much more exceptional observation, such as the telesystolic and protodiastolic adhesive pericarditis clicks, were recorded.

The use of an electrophonocardiographic unity of broad yield, concerning both frequency and intensity, showed one of us (P. C.) in a routine examination of the private practice, the unmistakable record of a pericardial friction, and, as the analysis proved some facts classically accepted and revealed some others, further observation was undertaken.

Although the number of cases is small, the uniformity of the results justifies following commentaries and conclusions.

CASE REPORTS

CASE 1.—A man, aged 63, old dietetically compensated diabetic, under the care of one of us for a year and a half, had angina pectoris spontaneously or when disturbed by the slightest emotion. With large doses of trinitrine (he had masticated about 3,000 pills) T₂ and T₃ were permanently negative. On April 18, 1941, in the early morning, there was a very severe midsternal pain; trinitrine was ineffective, and three 0.02 gr. morphium injections were required to stop the pain; the following day there were slight fever and a to-and-fro pericardial friction.

A simultaneous electrocardiogram and phonocardiogram (the first in three limbs derivations and IVF, the second in the four foci of auscultation using different filtration) showed electric alterations of a recent myocardial infarction (anterior type)

From the Cardiological Department of Buenos Aires Medical School (Semiological Institute, Prof. T. Padilla.)

Received for publication Jan. 2, 1942.

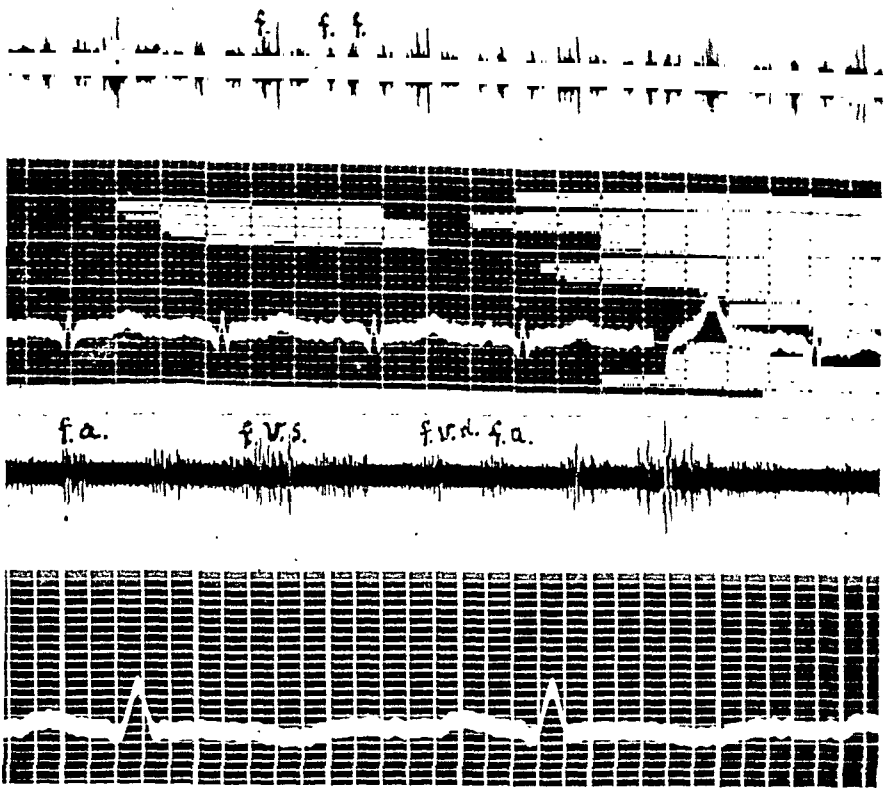


Fig. 1.—Stethoelectrocardiograms recorded at slow and high speed showing auricular (*f.a.*) ventricular systolic (*f.v.s.*), ventricular diastolic (*f.v.d.*) pericardial frictions of harmonical high pitch.

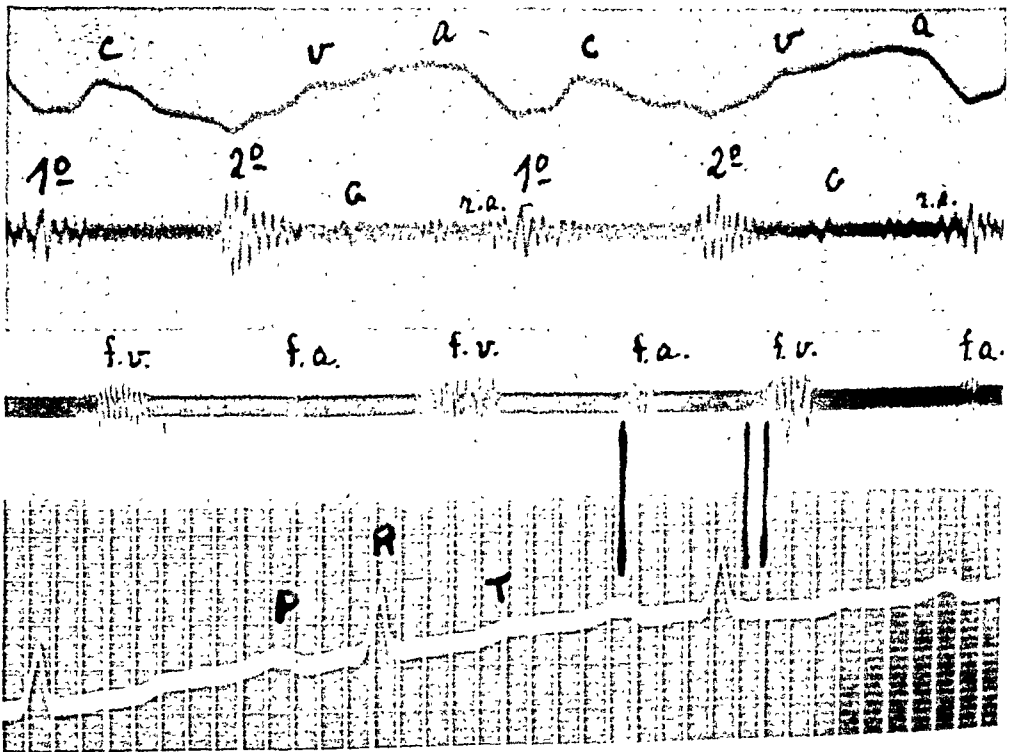


Fig. 2.—(Upper) Phlebostethogram, with accurate filtering for low pitch showing protodiastolic gallop rhythm and auricular sound before Brightlight pericarditis. (Down) Stethoelectrocardiogram, auricular (*f.a.*) and systolic ventricular (*f.v.*) pericardial frictions of harmonical high pitch.

and a series of more or less homogeneous high-pitched vibrations, exactly in the middle of systole, and protodiastole and presystole at the height of the P wave (Fig. 1).

CASE 2.—A man, aged 49, a physician, with chronic glomerulonephritis and hypertension and under the care of one of us (P. C.), had paroxysms of left ventricular failure and chronic uremia. On June 24, 1941, there was a Bright pericarditis with pericardial frictions rubs in to and fro, which could be heard and felt but with a much more intensive systolic element.

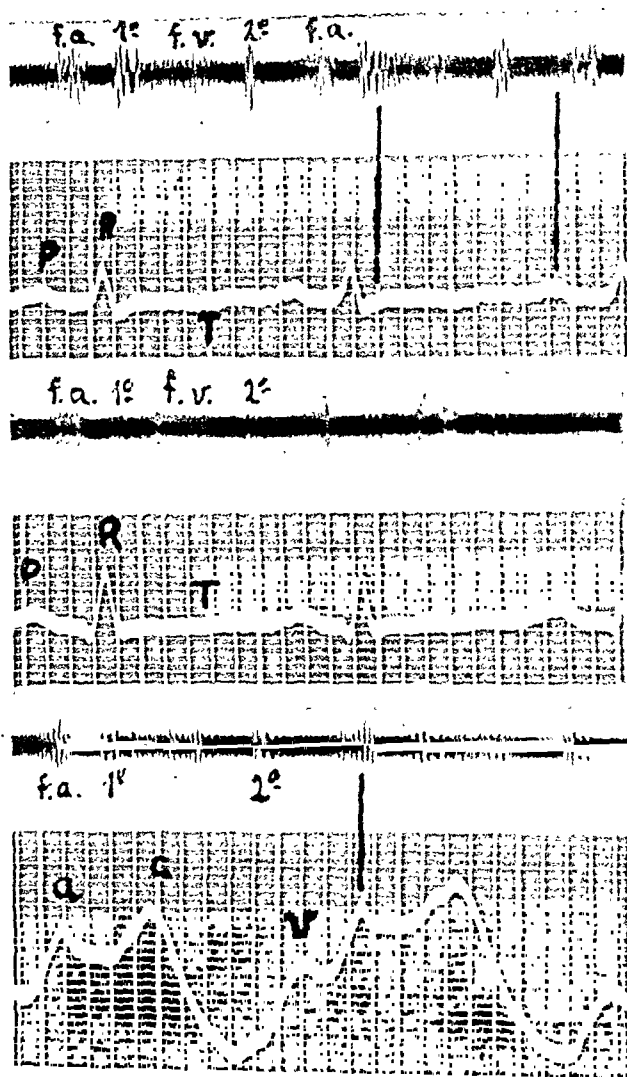


Fig. 3.—Stetho-phonocardiogram with different filterings showing auricular (f.a.) and ventricular systolic (f.v.) pericardial friction with harmonical high pitch.

The electrocardiogram of the three limb derivations and IVE, simultaneously recorded with the phonocardiogram of the four foci of auscultation with different filtration, showed left axis deviation with opponent S-T and T, and two groups of somewhat homogeneous high-pitched vibrations (the more important was in the middle systolic; the other, just at the height of the P wave) (Fig. 2).

CASE 3.—A woman, aged 45 years, with splenic anemia, was a patient at the Semiology Institute. A few days after the splenectomy, there were polyserositis

with negative T waves in all derivations and a to-and-fro pericardial friction. The phonocardiogram of the four foci of auscultation with different filtrations simultaneously registered with a derivation of the electrocardiogram or phlebogram showed, besides the fundamental heart noises, two groups of homogeneous vibrations; the first was systolic, longer, and more intense than the other group, which was smaller, beginning just at the height of the P wave and in the ascending branch of a.

CASE 4.—A man, aged 30 years, had polycystic kidney hypertension and uremia presenting an always marked protodiastolic gallop rhythm, often registered. There was a to-and-fro pericardial friction, by Bright pericarditis.

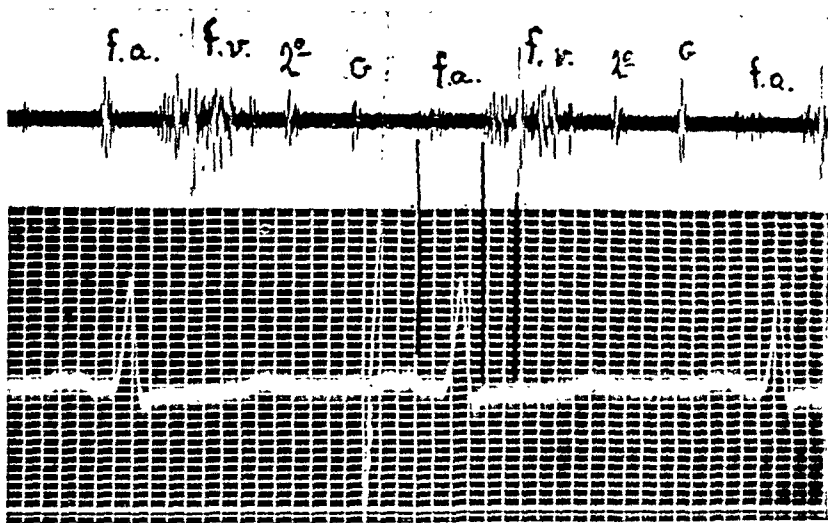


Fig. 4.—Sthethoelectrocardiogram showing the auricular (*f.a.*) and systolic ventricular (*f.v.*) pericardial friction. *2°*: second sound, *G*: gallop rhythm.

The phonoelectrocardiogram recorded by Dr. Campana, showed, besides the fundamental heart sounds and the protodiastolic gallop rhythm, evidence of two groups of somewhat homogeneous vibrations; the systolic one was lower and more intense, and the other was shorter and smaller, beginning just at the summit of the P wave (Fig. 4).

COMMENTS

Cullin⁷ (1824) described the pericardial friction sound; he compared it to a new leather rub (*craquement de cuir neuf*) and attributed it to the slipping of the abnormally dry pericardium.

Latham⁸ (1826) explains that the pericardiac friction sometimes does not show this acoustic character, seeming better a murmur because of friction of the unpolished pericardium.

Stokes⁹ (1833) revises these and other acoustic modalities of the friction sounds and shows, as an important characteristic, its variations in the postural changes.

Hope¹⁰ (1839) adds, as a fundamental characteristic, that the pericardiac friction is frequently a double to-and-fro noise, the first more intense than the second, in correspondence with the movements of the organ backward and forward within the pericardium during the cardiac cycle; but sometimes the noise may be only one, and then, systolic.

Pennoek¹¹ (1846) fixed and completed this knowledge verifying that the to-and-fro noises could be formed by three or four noises according with the pericardial friction produced by the consecutive and independent systolic and diastolic auricular and ventricular movements.

Sansom¹² (1850) states that the pressure exerted by the stethoscope on the precordium exaggerates the friction noises increasing the pericardial contact, but Walshe¹³ (1853) proves that it happens when the stethoscope pressure is adequate, for its excessive increase abolishes the pericardial rub explained by Friedreich¹⁴ (1873) as the result of the impairment of pericardial slipping.

The stethographic record of pericardial frictions shows the source of the to-and-fro noise and explains the intensity variations by the stethoscope's pressure.

The to-and-fro noise was proved to be double more frequently than triple. It happens that the most intensive and longer is always systolic, coincidently with the ventricular systole since it is a ventricular systolic friction. The other, or the remaining two, are diastolic; when only one is present, it is synchronic with the auricular systole, thus being an auricular friction; when there are two diastolic rubs, one is auricular and the other coincides with the rapid inflow, giving rise to a ventricular diastolic friction.

The incidence of the so-called ventricular frictions during the middle of the systole or maximum ejection phase and the protodiastole or rapid inflow shows that the pericardial rubs are in relationship to the maximal changes in volume and position of the ventricles with the consequent friction of the pericardium which covers them.

The verification that the so-called auricular friction noise coincides with the height of the auricular systole does not require more explanation than that the rubs are caused by the friction of the auricular pericardium and not the friction of the ventricular pericardium during the distention of these chambers by the blood coming from the auricle.

The verification that the to-and-fro noise of the auricular pericardial friction depends on the auricular systole suggests that, according to its production's time during the great silence, the conditions of the auricular-ventricular conduction can be deducted by the auscultation, as reported by Vedoya¹⁵ in an active rheumatic carditis with delayed auricular-ventricular conduction where the auricular friction was produced in the mid-diastole instead of the presystole.

The increase and disappearing of the friction of the noises by the stethoscope's pressure changes are explained by the graphic record.

The graphic registration of pericardiac frictions with different filtering showed them as acoustic phenomena composed of vibrations of different frequencies—some slow and others fast—generally with overtones taking more sound characteristics rather than noises, in opposition to the other cardiac acoustic phenomena.

The frequency of the stethoscope with the open bell is given by the lengthening of the skin enclosed within the stethoscope's edges—the more the lengthening the higher the frequency and vice versa. The lengthening depends upon the pressures exerted on the skin; the increase of the stethoscope's pressure increases the frequency (Rappaport and Sprague¹⁶). But further investigations (Cossio and Viale del Carril¹⁷) showed that the stethoscope's pressure (open bell) modifies not only frequency but amplification. In the progressive increase of pressure, initially there is more amplification with further damping.

Both stethoacoustic principles in connection with the pre-eminent high-pitched pericardial frictions help us to explain their changes, first *waxing* and then *waning* by a greater pressure of the stethoscope against the chest, without any relationship with thoracic deformations giving rise first to more contact and afterward to immobility of the pericardium.

The stethoscope pressing gently on the chest has a lower frequency than the prevailing pitch of the pericardial frictions, failing the transmission to the ear, aside from the masking produced by the predominating lower pitches upon the higher ones.

If the stethoscope exerts more pressure, its own frequency increases and picks up the friction noises; the transmission is better and thus the hearing improves not only because of a better transmission but also because of an inversely acting interference masking as a result of the pre-eminence of the higher pitches as compared with the lower ones.

If the stethoscope's pressure overlaps a critical level, the stethoscope's damping appears quickly, the transmission vanishes, and the pericardial frictions are barely heard or even are inaudible.

SUMMARY AND CONCLUSIONS

1. The graphic registration with different filtering of the pericardial friction rubs shows that it is an acoustic phenomenon more or less harmonic, and in which the relative high pitches prevail.

2. The acoustical characteristic so-called to-and-fro noise can be double or triple. It is more frequently double, the true to-and-fro. Of the two noises, the more intensive takes place during the ventricular systole (ventricular systolic friction); the other noise, the less intensive, is diastolic and is produced during the auricular systole because of the slipping of the pericardium covering these cavities (auricular friction). Less frequently it is triple; the most intensive noise is always systolic (ventricular systolic friction) and the other two are diastolic [one is the auricular friction, and the other is produced during the rapid inflow (ventricular diastolic friction)].

3. The primary waxing and consequently fainting or disappearing of the pericardial friction rub by the progressive increase of the stethoscope's pressure are explained by means of the frequency changes and damping of the stethoscope itself and not by thoracic deformation with more or less pericardial slipping.

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THE EFFECT OF HIGH ALTITUDE AND REBREATHING ON THE DURATION OF ELECTRICAL SYSTOLE IN MAN

M. S. WHITE, M.D., C. E. KOSSMANN, M.D., AND I. ERSHLER, M.D.
RANDOLPH FIELD, TEXAS

OF THE numerous studies on the effect of anoxia on the human electrocardiogram, few make reference to alterations in the duration of electrical systole (Q-T interval). Greene and Gilbert¹ found the "R-T interval" reduced in rebreathing experiments, but admitted that the measurements were difficult to make in many of their curves. Doetsch,² using a low-pressure chamber, measured the duration of the "P-T interval" on the ground and at a simulated altitude of 6,000 meters (19,685 feet). Obviously, this interval included a measurement of the auriculoventricular conduction time. In twenty normal subjects who were studied in the sitting position, the "P-T interval" remained the same in two, but was reduced in all the others from 0.01 to 0.12 second. The average reduction for the whole group was 0.031 second. In none of the work on the anoxemia test for coronary insufficiency³⁻⁶ is reference made to the duration of electrical systole.

For the purpose of ascertaining whether there are any alterations in the relation of electrical systole to cycle length during anoxic anoxia, six experiments were performed. All of the subjects were soldiers without a history of, or physical evidence of, heart disease. The thoracic roentgenogram was normal in every case. Records were made with an amplifier type of instrument.* In the experiments done during flight, the subjects were sitting; in those done on the rebreather, the subjects were recumbent.

Experiment I

The standard leads and Lead IVF were recorded on seventeen subjects during actual flights¹⁰ in army transports and bombers to a height of 20,000 feet. Ascent to the highest altitude was made in one to two hours; return to the ground was made in approximately one-half hour. The heart rates, the Q-T intervals, and the systolic indices of Bazett ($K = \frac{Q-T}{\sqrt{R-R}}$) were ascertained from the curves recorded on the ground prior to flight, at increments of 5,000 feet during flight, at

From the Department of Aviation Medicine, School of Aviation Medicine, Army Air Forces, Randolph Field, Texas.

Presented at the Thirteenth Annual Meeting of the Aero Medical Association of the United States, at Boston, Mass., Nov. 1, 1941.

Received for publication Feb. 4, 1942.

*General Electric, Model B, electrocardiograph.

TABLE I
EFFECT OF ASCENT IN ONE TO TWO HOURS TO 20,000 FEET ON HEART RATE, Q-T INTERVAL, AND SYSTOLIC INDEX IN SEVENTEEN NORMAL SUBJECTS

ALTITUDE (FEET)	RATE PER MINUTE				Q-T INTERVAL IN SECONDS				Q-T / $\sqrt{R-R}$			
	MIN.	MAX.	MEAN	STAND- ARD DEVI- ATION	COEFFI- ENT OF VARIA- TION	MIN.	MAX.	MEAN	STAND- ARD DEVI- ATION	COEFFI- ENT OF VARIA- TION	MIN.	MAX.
Ground	59	92	77.6	11.8	15.6	0.30	0.35	0.324	0.013	4.0	0.326	0.397
5,000	66	100	81.7	8.3	10.2	0.30	0.34	0.321	0.012	3.7	0.355	0.400
10,000	64	100	83.5	10.6	12.7	0.30	0.34	0.322	0.013	4.0	0.351	0.403
15,000	71	115	87.7	13.5	15.4	0.28	0.34	0.321	0.014	4.4	0.351	0.444
17,500	65	125	92.3	14.8	16.0	0.27	0.36	0.318	0.022	6.9	0.356	0.413
20,000*	69	115	91.3	13.0	14.2	0.29	0.34	0.318	0.015	4.7	0.360	0.423
20,000 with 100% oxygen*	48	103	65.2	13.8	21.2	0.30	0.41	0.356	0.029	8.1	0.365	0.394
Ground*	56	94	71.0	10.7	15.1	0.30	0.38	0.346	0.022	6.4	0.340	0.424
												0.3740
												0.0193

*Fifteen subjects.

17,500 feet, at 20,000 feet before and after breathing pure oxygen, and again on return to the ground.* In obtaining these values, an average of at least five complexes and cycles was used in each lead, and the average of all four leads was calculated for each subject.

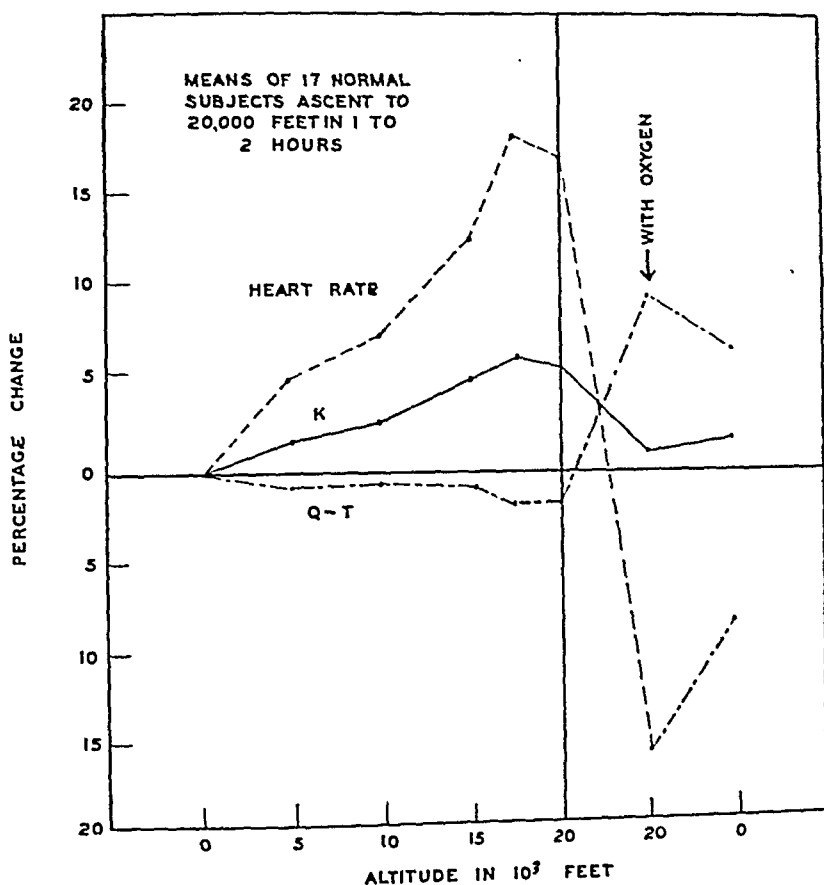


Fig. 1.

The means, standard deviations, and coefficients of variation for these measurements and for the calculated systolic indices were ascertained from the curves which were recorded at the various altitudes (Table I). These values were plotted in terms of the percentage change of the variables mentioned, with relation to the altitude in thousands of feet (Fig. 1). Observations at 20,000 feet, without oxygen, when compared to those made on the ground, showed a mean increase in pulse rate of 17.7 per cent, a mean decrease in the Q-T interval of 1.9 per cent, and a mean increase in the systolic index (K in figure) of 6.0 per cent. The difference between the mean of the systolic index calculated at ground level, and the mean of this index calculated at 20,000 feet, when divided by the standard error of this difference, gave a value of 3.1. This was interpreted to mean that the difference between the true means was reliable and probably greater than zero.

The average pulse rate decreased slightly at 20,000 feet, compared with what it was at 17,500 feet (Fig. 1). It will also be noted that

*Elevation at Randolph Field, 752 feet.

there was a sharp decrease of the pulse rate and an increase of the Q-T interval, as compared to the control levels, when oxygen was given at 20,000 feet. These did not return to normal even after landing, sixteen to fifty-six minutes later. However, in both instances the systolic index returned approximately to normal. Adequate explanations for these phenomena are at present lacking.

The individual records revealed that only one subject showed no change in the systolic index, while sixteen showed an increase. The greatest increase in this measurement at 20,000 feet, as compared with its value at ground level, was 0.045.

To summarize, in flight up to 20,000 feet the Q-T interval does not decrease in proportion to the increase in heart rate, with a consequent increase in the ratio: systole divided by the square root of the cycle length.

Experiment II

We wished to know whether electrical systole would change during flight if the pulse rate remained the same, or approximately the same. These conditions were created in sixteen normal subjects who were slowly flown up to 15,000 feet in approximately one and one-half hours, and maintained at that altitude for two hours. On ascent, the average pulse rate and the average Q-T interval remained practically constant. As the level was maintained at 15,000 feet, the pulse rate of the group gradually decreased and the length of electrical systole gradually increased, but the systolic index was unchanged. This experiment is not strictly comparable with the first, principally because of the lower altitude attained, but it does indicate that, up to 15,000 feet, provided there is no important change in pulse rate, the systolic index will remain constant.

Experiment III

The experiments were repeated with a modified rebreather designed by Major N. W. White, in which the utilized oxygen was replaced by nitrogen, and the carbon dioxide absorbed. In fourteen subjects, the four leads were recorded and measured as before, and the oxygen saturation of the ear blood ascertained by means of the photocell oximeter of Millikan.¹⁶ The same statistical constants were calculated, and the results were plotted as shown in Fig. 2. The Q-T interval, when the oxygen saturation of the ear blood was between 80 per cent and 77 per cent, was reduced 7.6 per cent, as compared to the control value. The pulse rate was increased 20.9 per cent; the systolic index was increased 4.5 per cent; and the fourth variable which could be ascertained, namely, the respiratory volume in liters per minute, corrected for dry gas at 0° C. and 760 mm. Hg, was increased 45 per cent. Compared to the altitude experiments, Q-T was reduced more than it was during flight, but the systolic index increased. In this instance, the increase was not statistically significant.

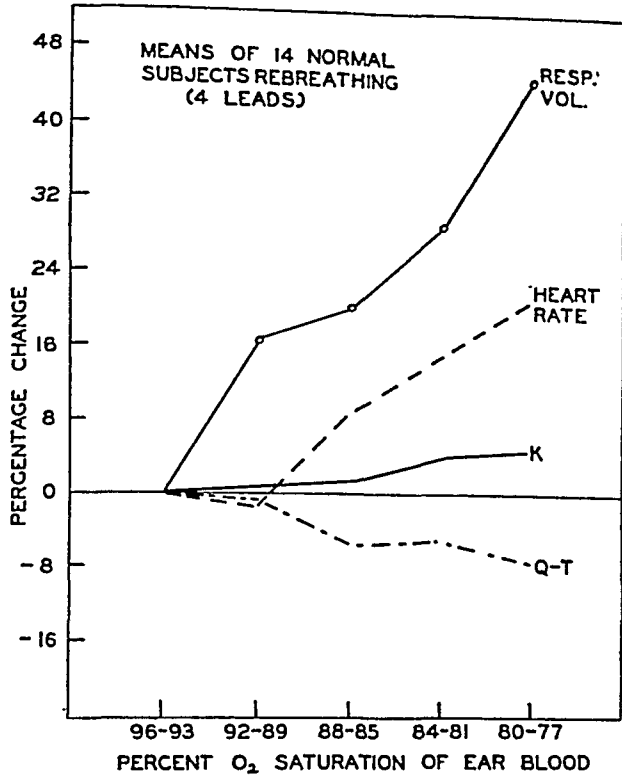


Fig. 2

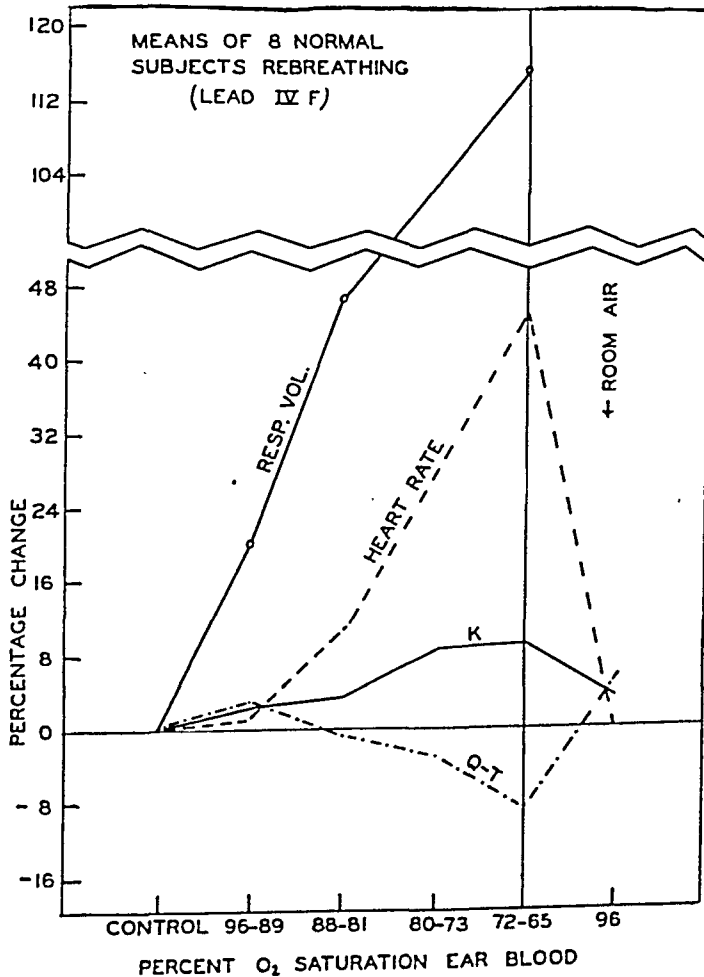


Fig. 3.

Experiment IV

In the previous experiment the oxygen saturation of the blood was reduced to a level between 80 per cent and 77 per cent, which is comparable to an altitude of approximately 15,000 to 16,000 feet. In another group of eight subjects, the oxygen saturation was reduced to 65 per cent (approximate, calculated altitude, 21,280 feet) while lead IV^F was being recorded. The results are shown in Fig. 3. The data on oxygen saturation are grouped rather grossly because a greater accuracy for the method of Millikan, especially at the lower saturations, is not claimed. The results bore out those obtained in flight and in the previous rebreathing experiment in which four leads were recorded. The average heart rate was increased 44.8 per cent; the average Q-T interval was reduced 9.0 per cent; and the average systolic index increased by a statistically significant 8.7 per cent. The respiratory volume, also measured in this instance, and corrected for dry air at 0° C. and 760 mm. Hg, showed an increase of 117 per cent.

The change in these variables was greater than during flight. The speed with which anoxia was induced was apparently the important reason for this difference. By rebreathing, an oxygen saturation of 65 per cent was attained in less than twenty-five minutes.

Experiment V

In all of the experiments described thus far, different normal subjects were used. For the purpose of controlling this variable, nine of the normal subjects, who had been previously studied on the rebreather with the four leads, were taken on a flight to 20,000 feet in approximately one and one-half to two hours. The results in this group were precisely the same as those obtained with the seventeen normal subjects in Experiment I.

Experiment VI

The effect of an increase in the pulse rate on the systolic index was studied in normal subjects on the ground. In order to increase the pulse rate, the use of drugs such as atropine and the nitrites was considered, but it was felt that their side actions made them undesirable for the purposes of this experiment. Judging from the literature, the results of exercise on the systolic index have been variable and confusing. Bazett⁵ calculated the systolic index in the electrocardiograms of three subjects who had been exercised by Lewis and Cotton. In two, the immediate change after exercise was a decrease, with a subsequent increase as the subject rested. Barker, Shrader, and Ronzoni⁶ did an exercise test on four subjects, which consisted of running up and down stairs until shortness of breath and fatigue were pronounced. This exercise was sufficient to reduce the pH and the carbon dioxide combining power of the blood, and to increase the lactic acid content. In

TABLE II

THE EFFECT OF RAPIDITY OF THE PULSE RATE INDUCED BY EXERCISE ON THE SYSTOLIC INDEX IN TEN NORMAL SUBJECTS

SUBJECT	RESTING			IMMEDIATELY AFTER EXERCISE			TWO MINUTES AFTER EXERCISE		
	Q-T	RATE	$\frac{Q-T}{\sqrt{R-R}}$	Q-T	RATE	$\frac{Q-T}{\sqrt{R-R}}$	Q-T	RATE	$\frac{Q-T}{\sqrt{R-R}}$
F-1	0.40	62	0.408	0.32	90	0.391	0.42	52	0.390
F-2	0.32	104	0.421	0.28	121	0.378	0.30	112	0.410
F-3	0.36	81	0.419	0.32	100	0.413	0.36	70	0.388
F-4	0.36	66	0.377	0.30	95	0.378	0.34	80	0.393
F-5	0.35	75	0.391	0.28	93	0.348	0.34	80	0.393
F-6	0.37	58	0.362	0.32	85	0.380	0.38	61	0.384
F-7	0.37	68	0.394	0.28	111	0.381	0.34	79	0.390
F-8	0.32	78	0.364	0.30	91	0.369	0.32	75	0.358
F-9	0.36	81	0.419	0.32	100	0.413	0.34	81	0.395
F-10	0.36	75	0.403	0.32	95	0.403	0.36	81	0.419
Means	0.357	74.8	0.3958	0.304	98.1	0.3854	0.350	77.1	0.3920
Percentage deviation from control				-14.8	+31.1	-2.6	-2.0	+3.1	-1.0

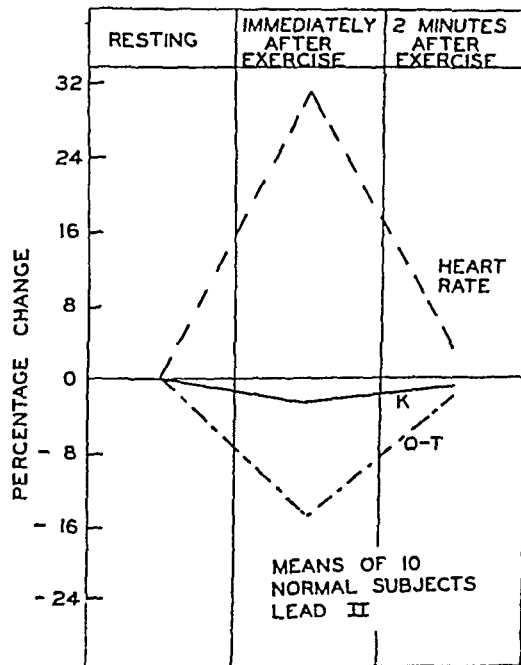


Fig. 4.

all four the systolic index was slightly increased immediately after exercise, and continued to be increased for an unspecified period after the exercise had been completed. Our intention was not to induce acidosis by exercise, but simply to produce an increase in the pulse rate. For this purpose, an exercise test, which consisted of hopping approximately one inch from the floor on one foot a hundred times in forty to fifty seconds, was done. With the subject recumbent, Lead II of the electrocardiogram was recorded as a control immediately after exercise, and again two minutes later. From the results shown in Table II and Fig. 4, it is clear that the average systolic index was immediately decreased,

and returned almost to normal two minutes after the exercise had been completed. Of the individual records, three showed a slightly increased index immediately after exercise; one was the same as the control; and the remaining six showed considerable decreases. Two minutes after exercise, four of the records showed a systolic index somewhat above the control value; the remaining six showed indices below the control value.

DISCUSSION

During anoxia, some change, probably chemical, is taking place in the muscle of the heart, and this opposes the shortening of the electrical recovery process that ordinarily occurs when the heart rate is increased. It is known that one of the ions in the blood serum which has a considerable effect on the duration of electrical systole is calcium. Any reduction of this circulating ion will result in a prolongation of the Q-T interval.^{17, 18} Since ventilation increases greatly during anoxia, it is possible that the ionized calcium is reduced by hyperventilation. This theory becomes more attractive when it is recalled that the low T waves during anoxia^{1, 10} are similar to those which occur with alkalosis.⁹ Data on the serum calcium at high altitudes are, however, conflicting. Goralewski¹¹ demonstrated slight decreases in blood calcium when oxygen deficiency was induced at normal atmospheric pressures. McFarland,¹² with a similar technique, found little change, either in normal or neurotic subjects, when an altitude of 18,000 feet was simulated. A conclusion on the importance of calcium does not seem possible without further investigation.

In Experiment I (Table I) the average systolic index of the seventeen men before flight was 0.3676. In only one instance was it greater than 0.392, which was the maximum observed by Bazett in fifteen normal men. In Experiment IV (Table II) the average systolic index of the ten men before exercise was 0.3958, and in six it was more than 0.392. The only difference in procedure in the two experiments was the posture of the subjects. In the former they were sitting; in the latter they were recumbent.

Cheer and Li¹⁹ found that a change in posture made a difference in the value of K. In seventy-five recumbent men the average value was 0.3741, and, in thirty-four other sitting men, it was 0.3698. This difference was not statistically significant. In Experiment III, control electrocardiograms were recorded on six subjects in both positions. When they were sitting, the average index was 0.3880, and when they were recumbent it was 0.3826. In two of the six it was shorter in the sitting posture.

The effect of different postures seems insufficient to explain the discrepancy between Experiments I and VI. A more probable explanation is inaccuracy of the time marker. A stroboscopic check on the timer indicated that it was probably operating incorrectly during Experiment

I. Although this makes the absolute measurements in this experiment unreliable, the relative changes are valid.

Systolic indices in excess of 0.392 have often been noted in normal male subjects by one of us (C. E. K.). The straight line regression formula calculated by Adams¹³ from his data on normal subjects persistently gave a longer duration for Q-T than similar formulae calculated from the data of Cheer and Li¹⁹ and of Fridericia.¹⁴ Larsen and Skúlason¹⁵ have confirmed the validity of Adams' formula. The discrepancy between these two groups of investigations also seems to be attributable to failure of the earlier workers to check the timing mechanism of their recording instruments.^{13, 15}

CONCLUSIONS

1. During anoxic anoxia induced by rebreathing or by flight into high altitudes, the ratio of the length of electrical systole to the square root of the cycle length is increased.

2. This increase occurs only when the pulse rate is increased, which means that it is the result principally of shortening of the cycle length without the expected shortening of the duration of systole.

3. With exercise of moderate amount, with the subject on the ground, the systolic index is, on the average, shorter immediately after exercise.

4. The conclusion reached is that anoxia opposes in some way those factors which, under normal conditions of oxygen tension, cause a decrease in length of electrical systole as the cycle length shortens.

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A STUDY OF THE ANALEPTIC VALUE OF CERTAIN DRUGS IN THE TREATMENT OF QUINIDINE DEPRESSION

S. A. WEISMAN, M.D.

MINNEAPOLIS, MINN.

PATIENTS who have been taking quinidine have occasionally died suddenly without apparent cause. Even post-mortem examination often shows no cause for such deaths. Death may have been the result of auricular and ventricular standstill, or of vascular or respiratory collapse.

It is known that quinidine, when given to dogs intravenously in large doses, causes a marked fall in blood pressure and a slowing of respiration. The blood pressure may continue to fall; the respiration may become very slow and finally cease. The heart, however, may continue to beat for several minutes after respiration ceases (Fig. 1). This confirms the observations of Barker and Levine¹⁶ and of Gordon, Matton, and Levine.¹⁷

The present study records data on the relative values of ten drugs which are used experimentally as analeptics in varying states of cardiovascular and respiratory depression caused by quinidine.

The drugs were divided into two groups for comparison as to their analeptic value. In Group I were coramine, picrotoxin, metrazol, and caffeine sodium benzoate. In Group II were benzedrine, paredrinol, paredrine, epinephrine, ephedrine, and neosynephrin.

Dogs were anesthetized with pentobarbital sodium, which was given intraperitoneally in doses of 35 mg. per kilogram of body weight. Quinidine was then administered intravenously in doses of varying size; 25 mg. per kilogram and less were considered small doses, and more than 25 mg. per kilogram was considered large. We found that 45 mg. of quinidine per kilogram was a sublethal dose.

From the Department of Medicine and the Department of Pharmacology, University of Minnesota.

This work was carried out with the aid of a grant from the Graduate School, University of Minnesota.

Part of the funds for carrying on the work were contributed by the Ciba Pharmaceutical Company.

Assistance in the preparation of this material was furnished by the personnel of Works Progress Administration, Official Project No. 665-71-3-69.

Received for publication Jan. 24, 1942.

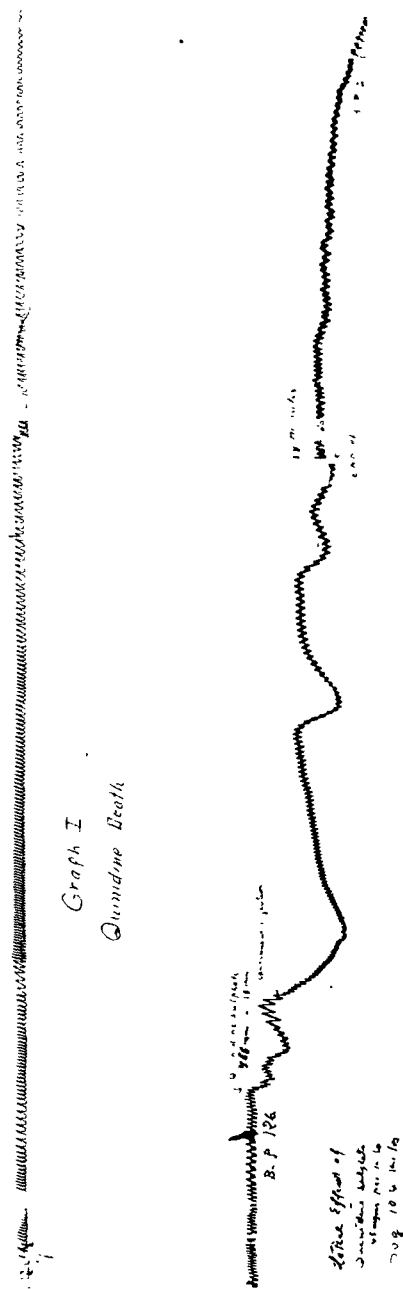


Fig. 1.—Effect of quinidine on the blood pressure. Upper tracing, respiration; lower tracing, blood pressure. Time marking, below, in seconds.

GROUP I

Coramine

(pyridine betacarboxylic acid diethylamide, 25 per cent solution)

Killian^{1, 2} and Barlow³ report that coramine will overcome light narcosis caused in rabbits by paraldehyde and avertin. Maloney and Tatum⁴ found coramine rather effective in counteracting the respiratory depressive effects of urethane, chloral hydrate, avertin, and ether, but it had little antidotal action against the barbiturates. Mousel and Essex⁵ found coramine without value in treating severe depression caused by pentothal sodium anesthesia in dogs, cats, and rabbits. Clinically, Wood⁶ reports definite respiratory benefits from the use of coramine in patients with marked depressive effects caused by avertin or surgical shock. He states that the toxicity of coramine is low, that it can be given intravenously in large doses, and that the dose can be repeated.

Table I gives the results of fourteen of our experiments in which coramine was given as an antidote after small, sublethal doses of quinidine had been given. We found that doses of 0.2 to 0.25 of coramine per kilogram were most effective. Smaller doses were ineffective and larger doses proved toxic.

Maloney,⁷ working with cats, found that amounts up to 150 mg. of coramine per kilogram had no demonstrable effect on animals that previously had been given 200 mg. of barbital per kilogram. Larger doses of coramine delayed recovery from the poisoning effects of barbital.

Burnstein and Rovenstine⁸ found amounts less than 5 c.c. only slightly effective or entirely ineffective in human beings who were under the effects of anesthetics or hypnotics, and advocated 5 c.c. doses, repeated, if needed, at five- to ten-minute intervals until 25 c.c. had been given. The intravenous route was most effective.

It will be noted that in our experiments the blood pressure always fell immediately after the administration of coramine; this was also shown by Maloney and Tatum⁴ and by Mousel and Essex.⁵ The blood pressure would tend to return to the previous level in about one minute or more. Sometimes the blood pressure would rise slightly above the previous level (Fig. 2).

Stoland and Ginsberg,⁹ working with heart-lung preparations and with intact dogs, found that coramine caused a fall in blood pressure and an increase in coronary flow.

In two of our experiments, when coramine was given after a sublethal dose of quinidine had been administered, the blood pressure continued to fall and the animals died. When smaller doses of quinidine had been administered, causing a fall of blood pressure not below 80 mm. Hg, coramine stimulated the respiratory center, as was manifested by an increase in depth and rate of respiration (Fig. 2). When large or

TABLE I
CORAMINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)		BLOOD PRESSURE		DOSE OF CORAMINE (C.C. PER KG.)	BLOOD PRESSURE		RESPIRATION	
		BEFORE	AFTER	BEFORE	AFTER		BEFORE	AFTER	BEFORE	AFTER
1	15.0	40.0	20	136	20	0.43	20	0	30"—died	
2	16.8	12.0	90	124	90	0.10	50	30 in 4'	25	19
3	10.0	46.0	50	140	50	0.15	50	92 in 38'	19	21
4	16.8	23.8	85	156	85	0.20	75	40 in 2' 45"		N.C.
5	13.8	43.0	42	150	42	0.70	42	N.C. in 7' 15"		N.C.
6	17.5	23.0	70	140	70	0.20	70	60 in 1' 50"		
7	18.1	44.0	8	92	8	0.20	8	80 in 6'	14	17
8	10.0	40.0	6	98	6	0.20	6	0 in 6'—died		N.C.
9	10.5	9.5	128	150	128	0.20	128	55 in 1'	16	44
10	9.5	10.0	120	160	120	0.20	120	70 in 17' 30"	14	18
11	9.7	10.0	130	160	130	0.20	120	0 in 108'	19	24
12	21.5	45.0	50	142	50	0.20	57	10 in 40' 15"	10	11
13	19.3	8.6	120	140	120	0.30	120	122 in 2'	-	-
14	19.3	45.0	56	130	56	0.30	56	144 in 17'	19	27
								114 in 2' 30"	18	21
								120 in 3' 30"		
								114 in 4' 30"		
								N.C. in 10'		
								42 in 1'		
								54 in 20'		
								118 in 2' 0"		
								(Rose to 130 in 5')		
								40 in 10'		

N.C., No change.

sublethal doses of quinidine had been given, causing a marked fall in blood pressure and a slowing of respiration, coramine sometimes added to the depression and proved fatal. Whitehead and Draper¹⁰ found that coramine almost doubled the mortality from an overdose of chloroform in dogs. Peters and Visscher,¹¹ using a heart-lung preparation, found that coramine produces, instead, dilatation of the heart, with decreased output and efficiency.

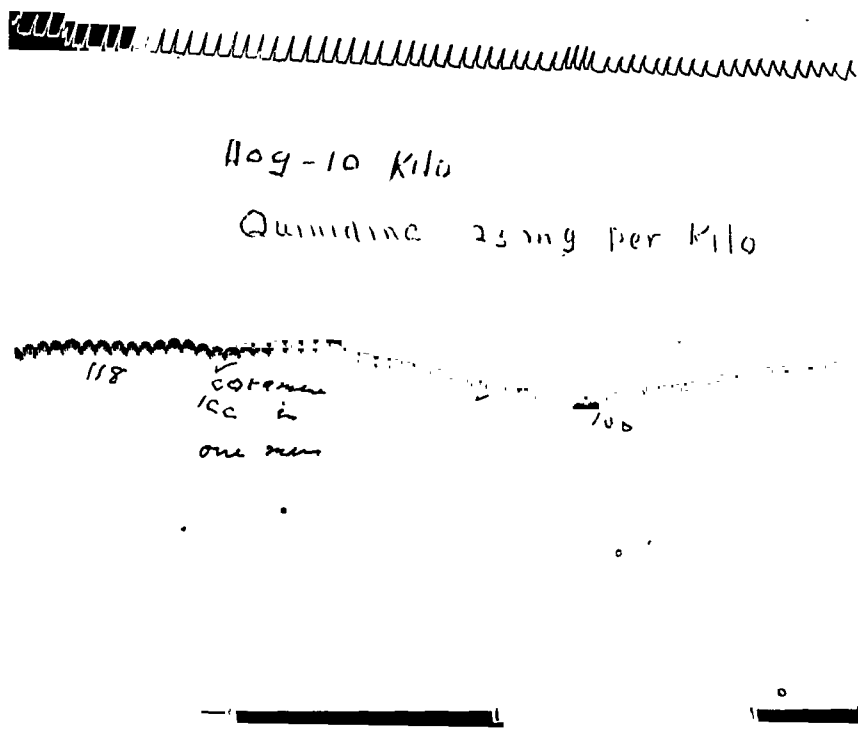


Fig. 2.—Effect of coramine on the blood pressure.

One must bear in mind that investigations made under conditions which differ in even a very slight degree may in all probability produce results that are not in complete harmony.

Picrotoxin

(a substance found in poison fish berries, *Cocculus indicus*)

Maloney, et al.,^{12, 13} experimenting with rabbits and dogs, found that picrotoxin, although it stimulated the respiratory mechanism, was definitely effective as an antidote in acute poisoning caused by the longer- and shorter-acting barbiturates.

Rice and Isenberger¹⁴ found that the drug shortened the duration of the respiratory paralysis produced in dogs by intracisternal injections of sodium amytal. Marshall, Walzl, and LeMessurier¹⁵ found that it was

TABLE II
Picrotoxin

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)		BLOOD PRESSURE		DOSE OF Picrotoxin (MG. PER KG.)	BLOOD PRESSURE		RESPIRATION	
		BEFORE	AFTER	BEFORE	AFTER		BEFORE	AFTER	BEFORE	AFTER
1	17.5	23.0	58	140	58	3.0	58	62 in 6'	Picrotoxin	Picrotoxin
2	18.6	10.8	90	150	90	3.0	100	96 in 2'		
3	18.6	21.0	58	140	58	6.0	58	100 in 6'	20	32 in 6'
4	18.6	38.0	70	150	70	3.0		68 in 6'	32	36 in 14'
5	18.6	45.0	68	150	68	6.0		N.C.	18	15 in 12'
6	21.5	45.0	48	140	48	6.0		N.C.		N.C.
7	10.0	46.0	70	140	70	3.0	70	78 in 4'	19	20
8	15.9	45.0	54	100	54	6.0	60	68 in 25'	20	27 in 25'
9	11.6	10.0	120	180	120	3.0	120	125 in 5'		N.C.
10	11.6	45.0	72	180	72	3.0	100	95 in 2'		N.C.
								100 in 1'		

N.C., No change.

TABLE III
Metrazol

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)		BLOOD PRESSURE		DOSE OF Metrazol (C.C. PER KG.)	BLOOD PRESSURE		RESPIRATION	
		BEFORE	AFTER	BEFORE	AFTER		BEFORE	AFTER	BEFORE	AFTER
1	10.4	10.0	88	140	88	0.13		N.C. in 7'	52	36
2	10.4	48.0	40	110	40	0.15	40	36 in 6'	35	24
3	12.0	8.6	120	140	120	0.2	120	138 in 3'	36	24
4	18.6	10.7	95	126	95	2.8	95	93 in 3'	26	33
5	12.0	45.0	40	140	40	0.3	44	43 in 8'	36	30
6	10.4	45.0	36	140	36	1.5	36	34 in 2'	35	34
								36 in 10'		

N.C., No change.

effective in dogs and cats against overdosage with chlorbutanol, paraldehyde, or "avertin fluid," and that it usually stimulated respiration in anesthetized animals in nonconvulsive doses. In a study of several analeptics, Barlow³ found it most effective in improving the respiration and circulation in rabbits, and in shortening the usual stages of recovery caused by sublethal doses of pentobarbital, chloral hydrate, and tribromethanol (avertin).

Mousel and Essex⁵ found picrotoxin without value in treating the depression caused by minimal lethal doses of pentothal sodium in dogs.

The results of our studies with this drug are shown in Table II. It will be observed that very little analeptic effect was obtained by using this drug after the administration of quinidine. However, when only small doses of quinidine had been used, the administration of picrotoxin did have a slight respiratory stimulating effect. There was no appreciable vascular effect.

Metrazol

(pentamethylene tetrazol)

Barlow³ found that, in rabbits, metrazol was an effective analeptic against sublethal and lethal doses of pentobarbital, chlorhydrate, and tribromethanol (avertin). He also found that its antidotal effect was in inverse proportion to the depth of the narcosis. No beneficial analeptic effects were obtained by Maloney and Tatum⁴ by giving metrazol to rabbits with barbiturate depression. Peters and Visseher¹¹ found that metrazol produced very little effect on the heart-lung preparation. Barker and Levine¹⁶ found that, in cats, cardiozol (metrazol) had little beneficial effect on the cardiovascular and respiratory depression caused by large doses of quinidine. Larger doses seemed to kill the animal promptly.

Table III shows the results of our study. Three dogs were given very small doses of quinidine, and three were given sublethal doses before the administration of metrazol. In only one case was there a rise in blood pressure, and this dog had received intravenously only 8.6 mg. of quinidine per kilogram, with a fall in blood pressure from 140 to only 120. In all other cases the blood pressure either fell or did not change. Respirations, however, seemed definitely improved.

Caffeine Sodium Benzoate

Gordon, Matton, and Levine,¹⁷ experimenting with cats, found caffeine sodium benzoate very effective in counteracting the depressive effects on respiration caused by large doses of quinidine. They found that about 5 mg. of caffeine sodium benzoate per kilogram, administered about the time when cessation of respiration seemed to be imminent, helped the return to normal breathing, but they found artificial respiration even more effective. However, caffeine sodium benzoate and artificial respiration together were more effective than either alone.

TABLE IV
CAFFEINE SODIUM BENZOATE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF CAF- FEINE SODIUM BENZOATE (MG. PER KG.)	BLOOD PRESSURE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE C. S. B.	AFTER C. S. B.	BEFORE C. S. B.	AFTER C. S. B.
1	10.0	46.0	140	40	5	40	60	18	19
2	11.4	17.5	102	35	10	35	24	18	24
3	18.1	45.0	92	22	5	22	14	20	21
4	12.0	8.6	138	110	5	110	128	23	46
5	12.0	45.0	128	70	5	70	45	42	44
6	30.4	33.0	92	25	5	25	54	20	23
7	18.6	21.0	146	68	5	68	12	20	32
							30		
							72		
							82		

C. S. B., Caffeine sodium benzoate.

Table IV shows the results of experiments on seven dogs. Six of these dogs received 5 mg. of caffeine sodium benzoate per kilogram, and one received 10 mg. per kilogram. The experiments showed that this drug was a very good respiratory stimulant and a slight cardiovascular stimulant when dogs had received only small doses of quinidine. However, as the dose of quinidine reached the sublethal and lethal quantity, which is 45 mg. or more per kilogram, caffeine proved to have only a slight beneficial effect on respiration. It acted better, however, than coramine and picrotoxin.

Summary of Group I Drugs

The drugs in this group as a whole had little beneficial effect as circulatory stimulants. They proved, however, to have some value as respiratory stimulants, especially after small doses of quinidine had been given. The order of effectiveness was as follows: metrazol, caffeine sodium benzoate, coramine, picrotoxin.

GROUP II

This group includes paredrinol, benzedrine, paredrine, epinephrine, ephedrine, and neosynphrin.

The characteristic action of this group of closely related chemical compounds (Fig. 3) is to increase the blood pressure. All of them are sympathomimetic drugs whose characteristic pharmacologic effects are similar to those produced by stimulation of the sympathetic nervous system. In order to discover what effect and relative value this group of drugs has as analeptics in marked cardiovascular and respiratory depression caused by toxic and sublethal doses of quinidine, we performed the following experiment.

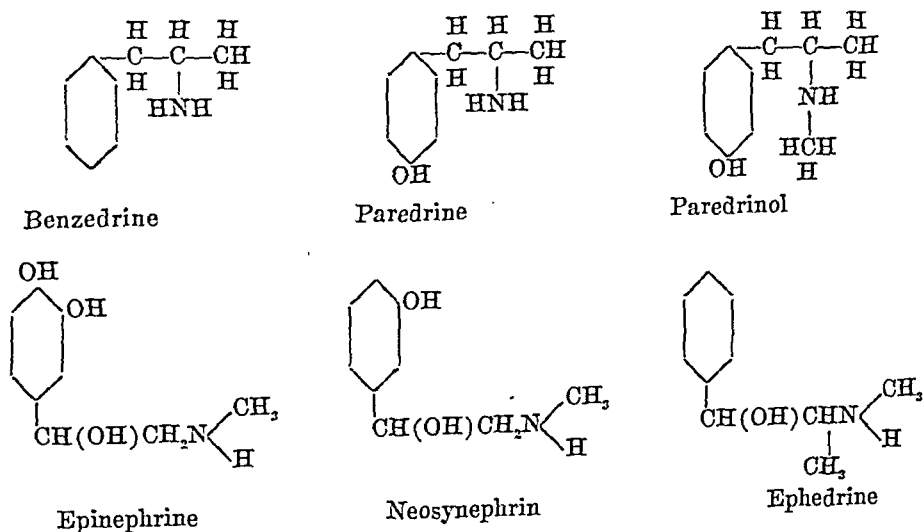


Fig. 3.

Dogs were anesthetized with pentothal sodium as in the previous experiments. Quinidine was given intravenously in small and in large doses. Tables V through X give the results of these studies.

After small doses of quinidine had been given, there was a marked rise in blood pressure after the administration of all these drugs. The rise in blood pressure was not so marked when the dose had been large. The exceptions were neosynephrin and epinephrine. Occasionally the blood pressure rise was greater after the administration of these drugs in the animals that had previously received large doses of quinidine. Tainter and Stockton¹⁵ found that after they had cocainized cats by their method, the response to a given dose of epinephrine was increased from 32 per cent in the control to 59 per cent.

The degree of rise in blood pressure, the time required for the blood pressure to reach its maximum, and the length of time the blood pressure remained elevated varied with each of these drugs.

Paredrinol

Paredrinol is the American trade name for racemic parahydroxy-alpha-*N*-dimethyl-phenethylamine, marketed in Europe under the name "Veritol." It is an isomer of ephedrine. Much has been written in the foreign literature on experimental and clinical studies of this drug. Colombi,¹⁹ in summing up the European literature on the beneficial effects of this compound on the circulation, states that they result from the following: (1) increased tone of the myocardium, (2) general arterial constriction, and (3) splanchnic constriction.

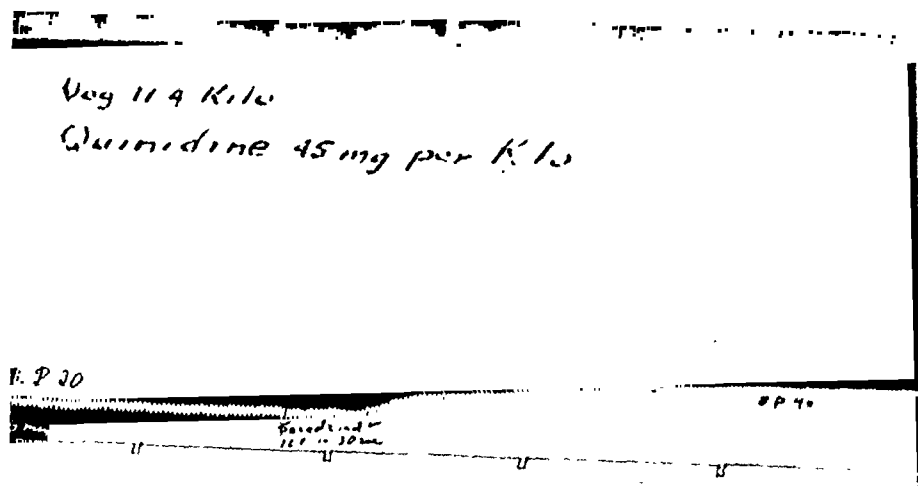


Fig. 4.—Effect of paredrinol after sublethal dose of quinidine.

In our experiments we found paredrinol fairly effective after small and large doses of quinidine had previously been given (Table V). The degree of blood pressure rise in response to paredrinol was less pronounced than in the case of paredrine. Paredrinol was, however, more effective than ephedrine (Fig. 4). The average blood pressure response after small and large doses had previously been given was very similar to

TABLE V
PAREDROLINOL

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF PAREDROLINOL (MG. PER KG.)	BLOOD PRESSURE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE PAREDROLINOL	AFTER PAREDROLINOL	BEFORE PAREDROLINOL	AFTER PAREDROLINOL
1	16.8	23.0	120	40	1.0	40	79 in 8' 20"	20	29
2	10.0	46.0	140	80	10 Total	80	90 in 7' 30"	25	24
3	17.5	23.0	140	74	10 Total	74	114 in 5' 30"		N.C.
4	14.1	28.3	114	50	0.42		Died within 1'		
5	9.7	10.3	120	78	1.9	78	160 in 3'	18	16
6	10.5	45.0	155	88	1.0	88	94 in 6'	8	7
7	10.5	45.0	128	55	1.0	70	90 in 22'	15	17
8	17.7	45.0	134	72	0.3	98	26 in 3' 30"	14	16
9	7.1	28.2	190	10	10 Total		Died within 1'		
10	12.7	8.6	155	128	1.0	128	154 in 3' 30"	24	26
11	12.7	45.0	138	60	1.0	60	80 in 3'		N.C.

N.C., No change.

TABLE VI
BENZEDRINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF BENZEDRINE (MG. PER KG.)	BLOOD PRESSURE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE BENZEDRINE	AFTER BENZEDRINE	BEFORE BENZEDRINE	AFTER BENZEDRINE
1	9.7	20.0	112	86	1.0	86	128 in 1' 30"	20	18
2	18.6	37.0	140	70	1.0	70	76 in 1'	23	24
3	10.45	57.0	138	50	0.94	50	70 in 30"	18	24
4	18.6	10.7	160	128	0.55	128	168 in 5' 30"	13	15
5	10.45	9.6	134	112	0.5	112	144 in 6' 30"	20	32
6	10.45	45.0	140	68	1.0	68	88 in 1'		N.C.
7	10.0	46.0	140	80	1.0	80	108 in 3' 30"	21	20
8	16.8	23.8	156	80	1.0	80	118 in 1' 30"	21	20
9	20.0	8.6	120	96	0.5	90	150 in 2'		N.C.
10	20.0	45.0	110	64	1.0	70	80 in 1' 30"		N.C.
11	9.7	30.0	116	60	1.0	65	74 in 1' 30"	-	-

N.C., No change.

almost epinephrine-like response. The maximum rise in blood pressure was reached in about one and one-half minutes, compared with over eight minutes with paredrinol, three minutes with paredrine, and four minutes with ephedrine.

Paredrine

Alles²⁰ showed that paredrine had about twice the pressor effect of benzedrine in dogs under the effects of barbital anesthesia. Lohman, Rinkel and Myerson²³ found paredrine more effective than benzedrine in raising the blood pressure of patients. Nathanson²⁴ reported a study on the comparative action of paredrine, ephedrine, and epinephrine on cardiac standstill induced by pressure on the carotid sinus. He found paredrine at least twice as effective as ephedrine. He also found that paredrine, although its action was less intense than that of epinephrine, was superior because of its prolonged effect.

In our studies, paredrine was definitely more effective than paredrinol and benzedrine. The rise in blood pressure with paredrine was twice that of the rise with the other two drugs after the dog was under the effect of large doses of quinidine (Table VII, Fig. 6). The group as a whole caused a slowing of the pulse rate. Respiration was not affected by paredrine. The effect of paredrine on the blood pressure lasted about an hour.

Ephedrine

The average rise in blood pressure after giving ephedrine to dogs that had previously received small doses of quinidine was 24.4 mm. This is less than one-half the blood pressure rise obtained by giving paredrine under similar conditions. Abbott and Henry²⁵ found that ephedrine was about half as potent as paredrine when given orally.

The average rise in blood pressure after giving ephedrine to dogs that had previously received large doses of quinidine was about 15 mm. Four of the ten dogs in this series died shortly after the administration of ephedrine. It seems that ephedrine was of little analeptic value after sublethal doses of quinidine, especially when the blood pressure fell after large doses of quinidine to about 28 mm. or less. The average rise in blood pressure caused by ephedrine in this group was about half the blood pressure rise from paredrine after sublethal doses of quinidine had been given. Of the drugs in this group, ephedrine caused the least rise in blood pressure (Fig. 7).

Epinephrine

Table IX gives the results of our study with epinephrine. There was a definite rise in blood pressure after this drug was given to dogs that previously had received small and sublethal doses of quinidine. The doses of epinephrine were from 0.001 c.c. per kilogram (the amount

TABLE VII
PAREDRINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF PAREDRINE (MG. PER KG.)	BLOOD PRESSURE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE PAREDRINE	AFTER PAREDRINE	BEFORE PAREDRINE	AFTER PAREDRINE
1	12.3	8.0	140	120	0.8	130	190 in 3' 35"	11	. 116
2	12.3	48.8	139	56	0.8	56	139	31	N.C.
3	21.0	45.0	120	36	0.5	36	72 in 1'		19
4	21.0	8.6	120	100	0.1	100	90 in 17'	7	6
5	12.3	8.1	134	92	10.0	92	170 in 3'	10	10
6	12.3	40.5	130	30	10.0	30	144 in 2' 45"	36	39
7	18.6	38.0	150	98	10.0	98	78 in 2' 55"	-	-

N.C., No change.

TABLE VIII

EPHEDRINE

DOG	WEIGHT (KG.)	DOSE OF QUINDINE (MG. PER KG.)		BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPHEDRINE (MG. PER KG.)		BLOOD PRESSURE		PULSE		RESPIRATION	
		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1	9.0	100	90 in 6'	182	156	27	22	1.0		90		132 in 1'		156	174	22	21
												108 in 6'		232	232		36
												104 in 24"		182	182		36
												106 in 40"		150	150		30
1	9.0	106	68 in 3'	150	150	30	30	2.5 5.5*		68 76		78 in 1'		150	252	30	34
												98 in 3'		208	208		31
												80 in 15'		246	246		48
												86 in 35'		240	240		84
2	14.5	130	100	176	138	19	12	1.0		100		120 in 30"		138	118	12	12
												No change in 15'		244	244		19
												N.C. in 30"		180	180		19
												172 in 30"		234	234		18
												124 in 15'		302	302		28
												126 in 30"		192	192		21
2	14.5	126	74	192	192	21	24	2.5		74		88 in 50"		192	174	24	25
												78 in 15'		260	260		30
												80 in 30"		200	200		23
3	15.8	100	82 end of inj.	140	126	17	15	0.25		82		100 in 1'		126	122	15	13
												110 in 5'			142		12
												120 in 55"			282		31
												114 in 5'			252		34
												110 in 15'			184		36
												110 in 30'			186		39
3	15.8	110	52 end of inj.	180	166	39	24	0.25		52		58		160	168	24	24
												60 5'			182		23
												66 15'			212		24
												68 1 hr.4'			136		150

*Five minutes later.

TABLE VIII—Cont'd

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)		BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPIEDRINE (MG. PER KG.)		BLOOD PRESSURE		PULSE		RESPIRATION	
		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
8	7.0	144	90							0.2		128 in 5'					
										0.4		134					
										0.8		150					
										1.0		154					
										2.0		172					
8	7.0	123	22							0.4							
										0.8							
										1.0							
										2.0							
										3.0							
9	9.5	142	76							Artificial respiration: died							
										0.2		76	80 in 1'45"				
										0.4		90	90				
										0.8		94	100 in 2"				
										1.0		84	92				
										2.0		88	108				
										3.0		90	108				
										4.0		98	122				
		104	28							0.4							
										2.0							
10	7.0	142	88							4.0							
										Artificial respiration: died							
										0.2		88	112 in 1'				
										0.3		112	122				
										0.4		122	146				
										0.5		146	136				
										0.6		134	148				
										0.7		148	150				
										0.8		132	158				
										0.9		158	160				
9	9.5									1.0		N.C.					
										2.0		N.C.					
										2.5		160	170				

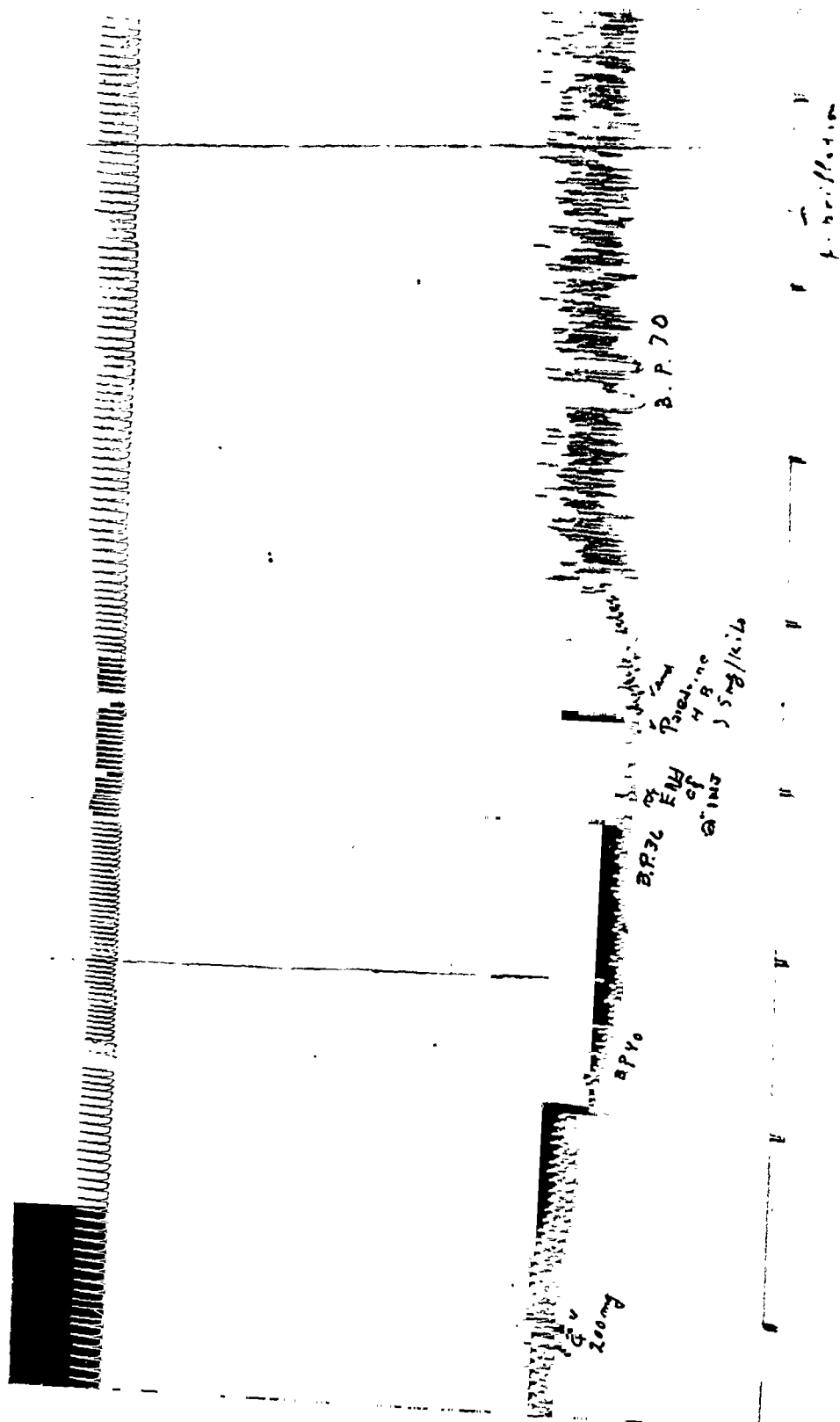


Fig. 6.—Effect of puredetine after sublethal dose of quinidine. Dog weight, 21.0 kg. Dose of quinidine, 15 mg. per kilogram.

TABLE IX
EPINEPHRINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPINEPHRINE (C.C. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1	17.0	10	106	92 in 3'	117	112	21	18	0.005	92	130 in 1' 92 in 15' 92 in 30" 110 in 1 hr.	112	122	18	18
1	17.0	45	110	62 end of inj.	80	100	21	24	0.005	62	72 in 30" 76 in 10' 78 in 15' 80 in 30'	100	137 114 106 124	24	23 23 27 24
2	14.6	10	155	100 in 4'	166	136	27	27	0.005	100	132 in 30" 110 in 15' 110 in 30' 114 in 1 hr.	136	138 162 150 150	27	31 27 26 38
2	14.6	45	120	46 in 4'	178	184	30	31	0.06	46	120 in 45" 46 in 5' 64 in 15' 70 in 30' 70 in 1 hr.	124	168 138 132 150 150	31	28 36 28 28 28
3	9.3	10	140	124 in 3'	180	166	19	13	0.005	124	154 in 55" 138 in 5' 134 in 15' 122 in 30'	166	140 132 128 168	13	17 11 10 15
3	9.3	45	146	38 end of inj.	170	60	13	15	0.06	38	128 in 1' 50 in 5' 58 in 15'	60	200 105 90	15	18 19 20

1 c.c. = 48.75 mg.

4	12.5	10	78	60				(0.001)	60 68 70 68 68 142 in 1' 15" 142 in 1' 30" 132 in 1'	80 in 30" 114 in 1' 118 in 45" 132 in 1' 142 in 1' 15" 142 in 1' 30" 132 in 1'					
4		20	78	60				0.001 0.001 0.002 0.003 0.004 0.005 0.006	60 58 54 56 56 60 62 62	65 in 10" 66 in 15" 60 in 10" 68 in 15" 70 in 30" 90 in 30" 98 in 1' 104 in 1'					
5	11.8	10	118	60				Neosyn. 0.001 0.002 0.003 0.004 0.005 0.006 0.007	60 70 64 82 90 120	75 in 15" 108 in 35" 118 in 40" 132 in 55" 148 in 1' 162 in 1'					
5		20	120	45				0.001 0.002 0.003 0.004 0.005 0.006 0.01 0.02	45 68 72 72 74 74 76 82	56 in 30" 72 in 30" 76 in 40" 88 in 30" 89 in 35" 92 in 35" 100 in 1' 108 in 1'					

TABLE IX—CONT'D

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPINEPHRINE (C.C. PER KG.)		BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
6	8.6	10	128	100					0.001		100	152 in 1'				
									0.002		132	162 in 1'				
									0.003		120	170 in 40"				
									0.004		110	182 in 1'				
6	8.6	45	116	30					0.005		110	210 in 1'				
									0.001		30	40 in 20"				
									0.002		36	80 in 45"				
									0.003		36	84 in 1'				
6	8.6	27	68	35					0.004		48	116 in 1'				
									0.005		80	130 in 45"				
									0.006		70	144 in 1'				
									0.03		35	96 in 1'				
8	11.8	10	106	90					0.002		38	52 in 20"				
									0.003		36	86 in 45"				
									0.004		44	106 in 1'				
									0.005		46	118 in 1'				
8	11.8	10	106	90					0.001		90	112 in 1'				
									0.002		106	114 in 55"				
									0.003		112	134 in 55"				
									0.004		110	120 in 1'				
8	11.8	10							0.005		110	148 in 45"				
									0.006		108	152 in 55"				

TABLE X
NEOSYNEPHIRIN

[illegible]

3	9.0	45	116	68 in 5'	182	118	18	18	0.06	68	178 in 1' 102 in 5' 76 in 15' 76 in 30' 70 in 1 hr. 15'	118	184 198 204 160 136	18	24 34 36 44 90
4	14.3	10	92	100 in 5'	150	100	9	9	0.005	100	210 in 1' 150 in 5' 100 in 35' 108 in 1 hr.	100	98 106 128 106	9	15 15 12 12
4	14.3	45	118	112 in 5'	106	174	14	22	0.03	112	270 in 35' 142 in 5' 162 in 10' 116 in 20' 122 in 30' 114 in 1 hr.	174	138 159 134 130 164 160	22	23 22 20 21 20 24
5	11.25	10	92	88 in 5'	200	122	28	18	0.005	88	180 in 1' 90 in 15' 110 in 30' 112 in 1 hr.	122	98 186 206 156	18	16 29 32 24
6	8.7	10	120	90					0.001 0.002 0.003	90 98 102	108 in 40" 160 in 55" 200 in 1'				
6		45	128	220					0.001 0.002 0.003 0.004 0.005 0.006	20 26 52 68 80 90	28 in 20" 48 in 35" 94 in 45" 130 in 45" 156 in 1' 170 in 1' 10"				
7		10	86	40					0.001 0.002 0.003	40 50 58	70 in 40" 104 in 55" 140 in 1' 10"				

TABLE X--CONT'D

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF NEOSYNE- PHRIN (C.C. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
7		45	82	28					0.001	28	34 in 15"				
									0.002	30	40 in 15"				
									0.003	34	50 in 20"				
									0.004	44	62 in 30"				
									0.005	50	78 in 35"				
									0.006	60	80 in 30"				
									0.007	64	104 in 55"				
									0.008	74	124 in 1'				
									0.009	86	142 in 1'				
									0.01	92	152 in 1'				
									0.02	90	158 in 1'				
									0.03	98	164 in 1'				
									0.001	65	108 in 1' 10"				
									0.002	86	174 in 1' 30"				
									0.001	20	64 in 1' 55"				
									0.002						
									0.003	50	72 in 35"				
									0.004	58	86 in 35"				
									0.005	62	98 in 40"				
									0.006	74	118 in 55"				
									0.007	82	138 in 55"				
									0.008	90	150 in 1'				
									0.009	96	158 in 1'				
									0.01	102	164 in 55"				
8	10.0	10	140	65					0.001						
									0.002						
									0.003						
									0.004						
									0.005						
									0.006						
									0.007						
									0.008						
									0.009						
8	10.0	45	120	20					0.001						
									0.002						
									0.003						
									0.004						
									0.005						
									0.006						
									0.007						
									0.008						
									0.009						
									0.01						

Note: Time interval between doses was ten to fifteen seconds.

used as a control) to 0.01 per kilogram. For comparing the analeptic value with that of the other drugs, we chose the experiments in which a dose of 0.005 per kilogram was used, or occasionally smaller amounts. In two of our earlier experiments—Dogs 2 and 3—in which sublethal doses of quinidine had been given, we gave large doses of ephedrine, i.e., 0.06 per kilogram.

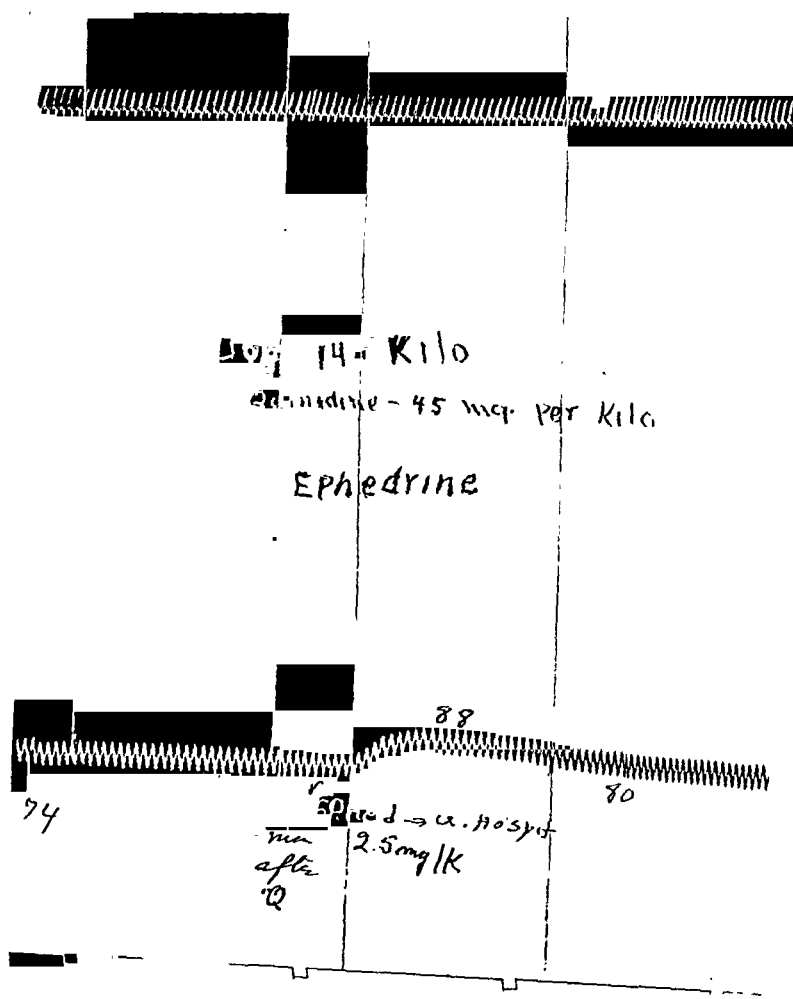


Fig. 7.—Effect of ephedrine after sublethal dose of quinidine.

The rise in blood pressure after epinephrine was, on the average, greater than in the case of any of the other drugs, with the exception of neosynephrin. However, when doses as small as 0.001 c.c. per kilogram were used, it appeared that epinephrine had a greater effect on the blood pressure than neosynephrin. The average rise in blood pressure after administering epinephrine to dogs that previously had received

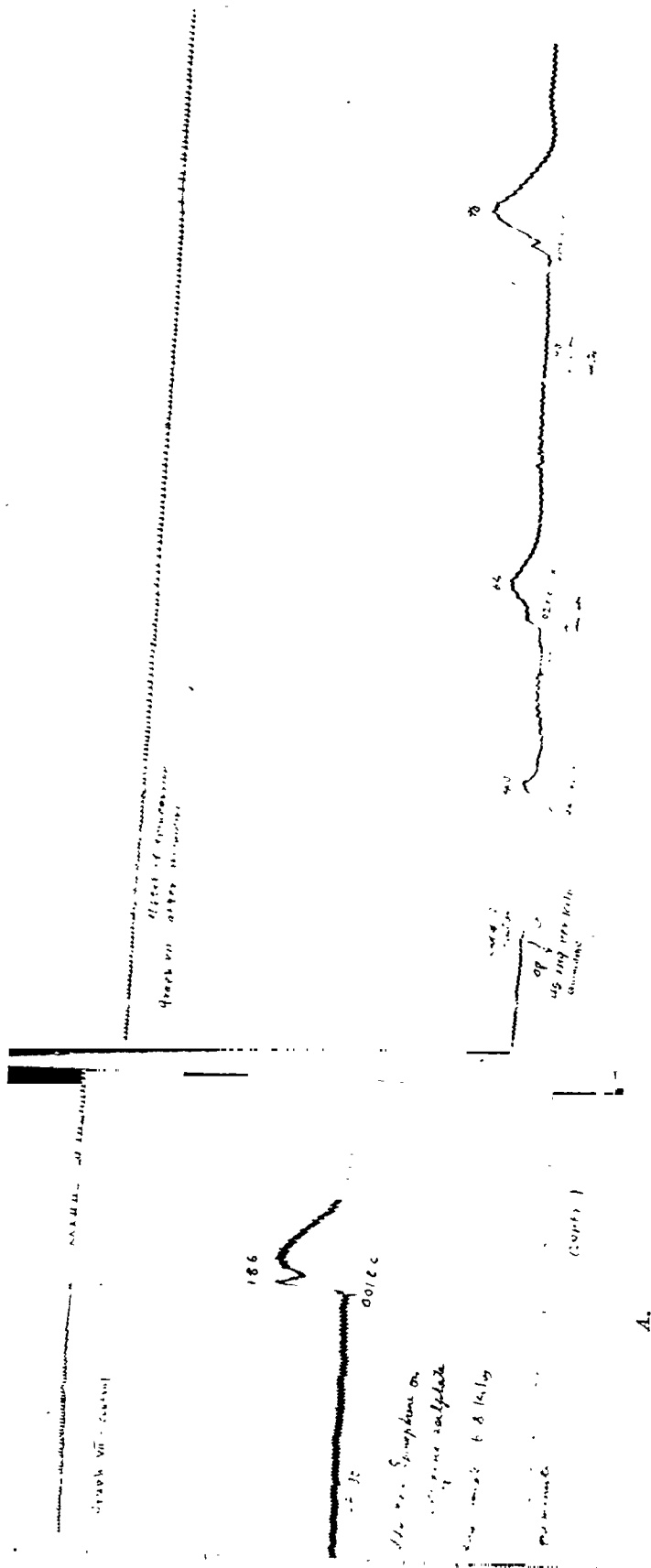


Fig. 8.—A, Control. B, After dog had been given 45 mg. of quinidine per kilogram.

small doses of quinidine was 46.8 mm. and 44.0 mm. in dogs that had been given sublethal doses of quinidine.

The maximum effect was fastest with epinephrine. The height of the blood pressure was reached, on the average, in fifty-three seconds in dogs that had previously received small doses of quinidine, and a little faster (forty-one seconds) in dogs that had received sublethal doses of quinidine (Table XI).

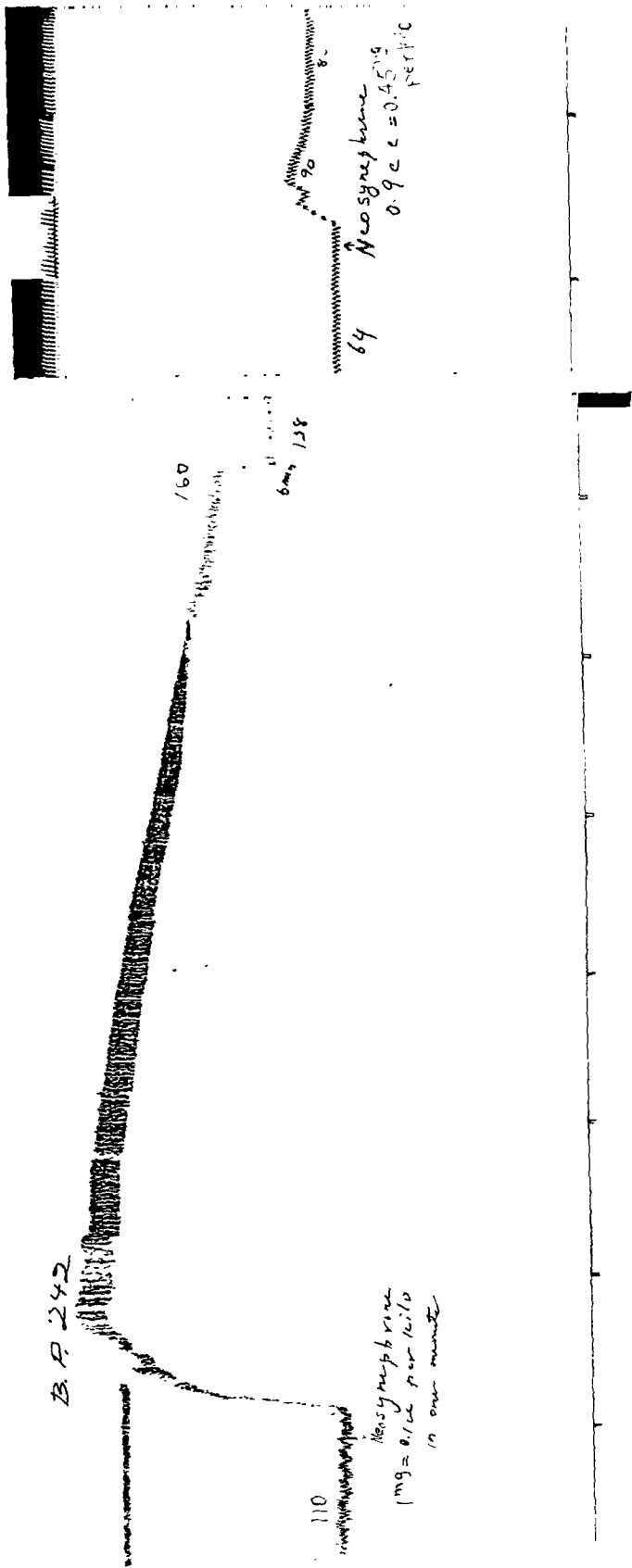
Neosynephrin

Neosynephrin hydrochloride is a levo-alpha-hydroxy-beta-methyl-amino-3-hydroxy-ethyl benzene hydrochloride. It is very closely related structurally to epinephrine.

The administration of this substance caused a greater rise in blood pressure than any of the others in this sympathomimetic group, both after the animals had previously been given small doses of quinidine and after they had received large doses (Table X). The next most effective drug was epinephrine, although epinephrine was about half as effective as neosynephrin when given to dogs that previously had received small or large doses of quinidine (Fig. 9).

Quinidine may affect the pressor response of these two drugs. Tainter and Stockton¹⁸ injected ergotamine intravenously into cats, in an average dose of 0.7 mg. per kilogram, which was enough to paralyze the sympathetic vasoconstrictors. The average control (a 48 per cent rise in blood pressure after epinephrine) was reversed to a fall of 21 per cent. The average control rise of 55 per cent after levo-meta-synephrin was decreased to an average rise of 21 per cent, but was not reversed. Ajazzi and Graubner²⁶ report that in the isolated rabbit's heart the paralyzing effect of quinidine on the heart is completely suppressed by neosynephrin, and particularly by epinephrine. Quinidine has the same inhibiting action against neosynephrin which makes these drugs mutually antagonistic.

In a few experiments, in which larger doses of neosynephrin and epinephrine were used, the difference in response between these two drugs was not so pronounced; however, neosynephrin caused a definitely greater pressor response. The pressor effect of neosynephrin lasted about fifteen minutes, whereas the pressor effect of epinephrine lasted less than half that time. In this study we did not observe the consistent slowing of the heart rate reported by Johnson,²⁷ Keys and Violante^{28, 29} Bittrich,³⁰ and Lorhan and Oliverio.³¹ The maximum rise in blood pressure from neosynephrin in our experiments was reached, on the average, in fifty-eight seconds after small doses of quinidine had previously been given, and fifty-five seconds after sublethal doses of quinidine had previously been given. Epinephrine acted a little faster, i.e., fifty-three seconds after small doses of quinidine and forty-one seconds after sublethal doses of quinidine.



A.

B.

Fig. 9.—Effect of neosynephrin after sublethal doses of quinidine. A, 1 mg. of neosynephrin per kilogram after 37.6 mg. of quinidine per kilogram. B, 0.45 mg. of neosynephrin per kilogram after 50 mg. of quinidine per kilogram.

CONCLUSIONS

1. Coramine, pierotoxin, metrazol, and caffeine sodium benzoate were of some value as respiratory stimulants when depression of the cardiovascular and respiratory systems had been induced by small doses of quinidine.

TABLE XI

	AV. RISE IN BLOOD PRESSURE AFTER				AV. TIME FOR MAXIMUM RISE OF BLOOD PRESSURE AFTER			
	SMALL DOSE QUINIDINE		LARGE DOSE QUINIDINE		SMALL DOSE QUINIDINE		LARGE DOSE QUINIDINE	
Benzedrine	40 mm. (av.)	42 40 32 34 38	17 mm. (av.)	20 20 28 20 9 6	348" (av.)	130" 550" 650" 200" 130"	130" (av.)	100" 650" 100" 250" 150" 100"
Paredrinol	42 mm. (av.)	39 40 62 26	16 mm. (av.)	16 6 20 26 20	335" (av.)	820" 550" 200" 550"	848" (av.)	750" 100" 600" 1200" 3200" 100" 200"
Paredrine	64 mm. (av.)	70 70 52	29.5 mm. (av.)	16 34 48 20	347" (av.)	335" 270" 345"	348" (av.)	700" 100" 255" 200"
Ephedrine	25.8 mm. (av.)	42 20 18 20 50 26 14 34 10 24	14.5 mm. (av.)	16 14 14 28 12 Diol Diol Diol 9	154" (av.)	150" 650" 160" 150" 550" 150" 100" 550" 200" 100"	420" (av.)	100" 650" 1500" 2500" 500"
Neosynph- rin	88.5 mm. (av.)	78 60 100 110 92 98 82 88	84 mm. (av.)	100 110 118 118 76 28 36	58" (av.)	100" 645" 100" 100" 660" 140" 630"	45" (av.)	150" 100" 100" 635" 100" 635" 140"
Epinephrine	46.8 mm. (av.)	38 32 30 100 38 74 15 58 30 53	44 mm. (av.)	10 74 90 8 2 50 72	655" (av.)	100" 630" 655" 650" 645" 130" 635" 100" 630" 660"	644" (av.)	650" 646" 100" 630" 620" 645" 100"

2. The order of effectiveness of these drugs as respiratory stimulants in light quinidine depression was as follows: metrazol, caffeine sodium benzoate, coramine, pierotoxin.

3. After large doses of quinidine, depression was often aggravated by metrazol, coramine, and picrotoxin.

4. Paredrinol, ephedrine, benzedrine, paredrine, epinephrine, and neosynephrin showed definite value as circulatory stimulants, after both small and sublethal doses of quinidine (Table XI).

5. Ephedrine, epinephrine, and benzedrine also showed definite respiratory effects. There was some evidence that paredrinol produced respiratory stimulation, although very little.

6. Ephedrine was the least effective in counteracting the circulatory depression caused by small or large doses of quinidine.

7. The effect of benzedrine and paredrinol on the blood pressure rise was very much the same; however, the time of appearance of the maximum rise in blood pressure after the administration of these drugs was definitely much shorter after giving benzedrine.

8. The effect of neosynephrin lasted twice as long as that of epinephrine.

9. Paredrine was one of the most valuable pressor substances in this group. It was about twice as effective as ephedrine, benzedrine, or paredrinol. Although the blood pressure response was much less after its administration, compared to that to epinephrine and neosynephrin, the effect of paredrine lasted much longer.

10. The most effective pressor substance in this group was neosynephrin. The blood pressure response was about twice as high, and the effect lasted twice as long after giving neosynephrin as after administering epinephrine, after both small and large doses of quinidine.

I wish to express my sincere appreciation to Dr. A. D. Hirschfelder for his valuable suggestions and cooperation in carrying out the experiments described in this paper and, also, to Mr. G. Tamcales, for his technical assistance.

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Department of Clinical Reports

VENTRICULAR TACHYCARDIA STOPPED ON THE TWENTY-FIRST DAY BY GIVING QUINIDINE SULFATE INTRAVENOUSLY

REPORT OF A CASE

ALFRED W. DUBBS, M.D., AND DAVID H. PARMET, M.D.
ALLENTOWN, PA.

THE following report describes a case of ventricular tachycardia which occurred in a patient who was subject to attacks of bronchial asthma. The tachycardia followed the administration of epinephrine in oil, and continued without interruption for twenty-one days. Quinidine sulfate, administered intravenously,¹ caused immediate and dramatic cessation of the tachycardia.

CASE REPORT

S. B., a white man, aged 52, was admitted to the Sacred Heart Hospital complaining chiefly of a fluttering sensation in the epigastrium. This symptom had appeared suddenly two days previously and persisted without interruption. The patient had always enjoyed good health except for periodic attacks of bronchial asthma. These attacks, which had appeared irregularly for the preceding three years, always responded promptly to the administration of ephedrine by mouth.

On the evening prior to the onset of the above complaint, the patient was seized with an attack of asthma. The family physician was called, and, instead of prescribing the usual dose of ephedrine, epinephrine suspended in oil was administered parenterally. The asthma subsided; the patient fell asleep; and, the following morning, upon awakening, he noted a fluttering sensation in the epigastrium, accompanied by a feeling of nausea. His physician was again called, and the chief abnormality was a tachycardia with a rate of 180 beats per minute. Two days later, after there had been no response to sedation, vagal stimulation, and precordial ice cap, the patient was admitted to the hospital.

Physical examination upon admission revealed a white man who was lying comfortably in bed. A few scattered râles at the bases of the lungs and a tachycardia with a rate of 170 beats per minute were the only objective signs. The blood pressure was 90/58. Shortly after admission the patient complained of inability to void, and catheterization was done. It was necessary to continue this procedure throughout the course of the illness. The blood cell counts were normal. The urine was negative except for a slight trace of albumin. The blood Wassermann reaction was negative. The electrocardiogram (Fig. 14) revealed a tachycardia which was interpreted as being ventricular in origin.

The patient was given 25 grains of quinidine sulfate by mouth daily, starting on the third day of the tachycardia, and this was continued for one week with no effect. On the tenth day of the disease the patient began to have symptoms of

From the Department of Electrocardiography, Sacred Heart Hospital.
Received for publication Dec. 26, 1940.

congestive failure. There were signs of fluid in the right pleural sac, and the edge of the liver extended below the costal margin and was definitely tender. The right side of the chest was tapped on four occasions between the twelfth and twenty-first day of the disease, and a total of 4,610 c.c. of transudate was removed.

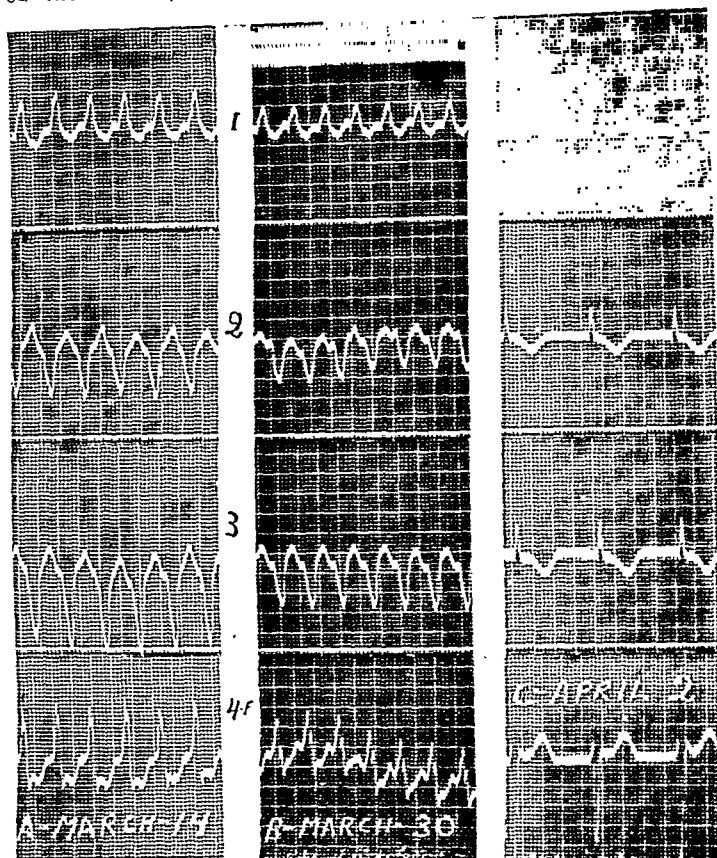


Fig. 1.—A and B, Electrocardiograms taken during the paroxysm of ventricular tachycardia. C, Electrocardiogram taken fifteen minutes after cessation of the tachycardia.

Digitalis was started on the tenth day, and a sufficient quantity was given to cause complete digitalization, but there was no effect on the heart rate or congestive signs and symptoms. Eserine sulfate was started at the same time, in 1.4 gr. doses three times a day, and stopped after a day's trial because of nausea and vomiting. On the twelfth day aminophyllin in $3\frac{1}{2}$ gr. doses was given intravenously every four hours, and oxygen by nasal catheter was started. The former had no effect upon any of the patient's symptoms, and was discontinued. The oxygen was given throughout the remainder of the illness. On the fourteenth day 0.25 mg. of mecholyt was given subcutaneously. This was immediately followed by a generalized flush, sweating, a sense of tightness in the chest, and nausea and vomiting. We realized that mecholyt is used primarily to control the auricular type of tachycardia, but felt that a trial was warranted. It had no effect upon the cardiac rate in this case. On the seventeenth day quinine dihydrochloride (5 grains in 25 c.c. of normal saline) was administered intravenously with no change. On the eighteenth day 2 c.c. of a 50 per cent solution of magnesium sulfate were given intravenously with no effect. The electrocardiogram (Fig. 1B) on the nineteenth day of the tachycardia was essentially the same as the previous tracing.

The patient rapidly became weaker and a state of shock supervened. His mental attitude changed from one of cooperation to marked apathy and despondency.

Food was refused and death was welcomed. The signs of congestive failure increased. There were cyanosis, orthopnea, recurring effusion in the right pleural sac, coarse râles at the base of the left lung, and a tender liver edge 4 finger-breadths below the costal margin. The abdomen was moderately distended, and the urinary retention persisted.

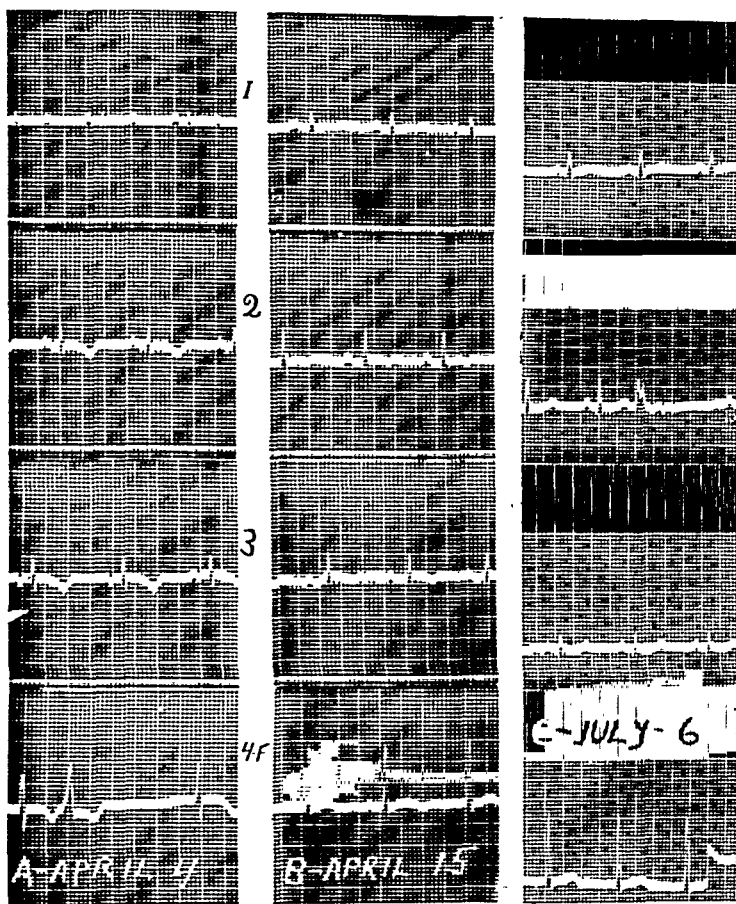


Fig. 2.—A, B, and C, Electrocardiograms taken after cessation of the tachycardia.

On the twenty-first day, when hope for the patient's recovery was practically exhausted, 15 grains of quinidine sulfate, dissolved in 90 c.c. of sterile distilled water, were administered intravenously. Prior to this the apex rate was 148 per minute and the blood pressure was 92/80. Half of the above solution had entered the vein when the rate suddenly fell to 68 per minute and the blood pressure rose to 106/74. The change in the patient was just as spectacular. He immediately became alert and expressed an interest in what was happening. His general state changed from one of extreme apathy to one of relative brightness. There was a moderate amount of nausea and vomiting immediately after the drug was given, but this rapidly subsided. His recovery from this point was continuous, uneventful, and apparently complete. An electrocardiogram (Fig. 1C) which was taken fifteen minutes after the rate change showed nodal rhythm and a ventricular rate of 80. The patient continued to take 5 grains of quinidine sulfate by mouth three times a day for one week after the cessation of the tachycardia.

DISCUSSION

The authors felt that reporting this case was justifiable if only to bring to the attention of the reader, not a new method²⁻⁵ of treatment

for ventricular tachycardia, but one that they feel is too frequently referred to as a measure of last resort. In this case it was undoubtedly life saving, and, had it been used sooner, there is no reason to believe that the results would not have been the same.

Prior to the intravenous administration of quinidine sulfate the drug had been given in large doses by mouth with no effect. In addition, there was no response to numerous other preparations which have been suggested as means of controlling this form of tachycardia.

With the report we present a series of electrocardiograms (Figs. 1 and 2) which were taken during the course of the tachycardia and after it ceased. The tracing immediately after cessation of the tachycardia (Fig. 1C) is of particular interest because of the conduction and T-wave changes. The rhythm (Fig. 1C) after the disappearance of tachycardia was nodal. This rapidly changed to normal sinus rhythm (Fig. 2A). The T-wave changes in Leads II and III (Fig. 1C) apparently were not the result of a recent myocardial accident, for the change from marked inversion to a more normal form (Fig. 2A, B, and C) was quite rapid. In addition, the rapid clinical improvement after cessation of the tachycardia would seem to be additional evidence that this is so. The change in the rhythm and inversion of the T waves of this character very likely reflect extreme myocardial fatigue and exhaustion, resulting from the long-continued tachycardia. McMillan and Bellet⁶ observed similar T-wave changes in the electrocardiogram of a 16-year-old girl after a paroxysm of ventricular tachycardia. They were of the opinion that the heart in their case was undamaged. The flattened T waves in Lead I (Fig. 2A, B, and C), together with an occasional ventricular extrasystole, suggest some myocardial abnormality in our case, and this may have been a factor in initiating the tachycardia.

CONCLUSION

A case of ventricular tachycardia which was stopped on the twenty-first day of the paroxysm by the administration of quinidine sulfate intravenously is reported.

Electrocardiograms taken during the tachycardia and afterward, showing interesting conduction and T-wave changes, are included.

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Department of Reviews and Abstracts

Selected Abstracts

Caeiro, A.: Velocity of Propagation of the Different Waves of the Venous Pulse.
Rev. argent. de cardiol. 8: 329, 1941.

Velocity of propagation of the different waves of the venous pulse were measured in the dog with an efficient method. In general their propagation is much slower than those of the arterial pulse. The averages vary between 0.85 and 4.69 per second, the different accidents of the venous pulse having different velocities of propagation.

The beginning of the v wave, being a stagnation phenomenon, propagates very slowly (0.85 m. per second). The apex of the v wave which is purely a pressure variation propagates much more rapidly (3.86 m. per second). The beginning apex and end of a and the end of v which represent a mixture of pressure and volume variations have a medium velocity of propagation (1.39, 1.4, and 1.24 m. per second, respectively). Of the accidents of the venous pulse which are not properly of venous origin, the second sound is the more rapidly propagated due to its proper physical characteristic (4.69 m. per second). The c wave has a velocity of propagation which statistically can be considered as equal to that of the mixed waves already mentioned (1.68 m. per second).

AUTHOR.

Hahn, P.: Does the Heart Work as a Pressure Pump or as a Hydraulic Ram?
Cardiologia 5: 308, 1941.

The author discusses Havlíček's theory comparing the heart to a hydraulic ram and gives his reasons for being unable to accept that theory.

AUTHOR.

Sigler, L. H.: The Hyperactive Cardioinhibitory Carotid-Sinus Reflex as an Aid in the Diagnosis of Coronary Disease. Its Value Compared With That of the Electrocardiogram. *New England J. Med.* 226: 46, 1942.

A comparative study is presented of the incidence of a hyperactive cardioinhibitory carotid-sinus reflex and of electrocardiographic abnormalities in a series of 1,073 cases, mostly ambulatory, of coronary disease. It was found that 91.3 per cent of the males and 72.6 of the females in this series showed the cardioinhibitory response, whereas only 63 per cent of the males and 71.9 of the females showed abnormalities in the electrocardiogram. High degrees of cardioinhibitory response, which are definitely abnormal, occurred in 61.8 per cent of the males, and 42.9 per cent of the females. Marked electrocardiographic abnormalities occurred in only 37.4 per cent of the males and in 40 per cent of the females.

It is believed that the hyperactive cardioinhibitory carotid-sinus reflex may be used as an aid in the diagnosis of coronary disease in persons of the coronary age who present suspicious complaints. As such, it is often of greater value than the

electrocardiogram, and will suggest the correctness of the diagnosis when the electrocardiogram may be entirely misleading.

The explanation for the frequency of the hyperactive reflex in coronary disease is, at the present state of knowledge, purely theoretical. It may be due to local ischemia in the heart, which lowers the resistance in the vagal ganglions and in the myoneural junctions, or which produces some chemical changes that sensitize the vagus nerves locally.

AUTHOR.

De Soldati, L., Cabanne, E. A., and Introzzi, A. S.: Determination of Blood Flow of the Fingers by the Plethysmographic Method. *Rev. argent. de cardiol.* 8: 383, 1942.

The blood flow through the fingers was recorded by the plethysmographic method in normal subjects and the influence of diverse stimuli was studied.

Immersion of both legs in cold water (15° C.) produced after a few minutes, first a decrease and then an increase in the blood flow which continued until after twenty minutes it reached the double of its initial value. Simultaneously a slight increase of the buccal temperature and a slight decrease of the cutaneous temperature occurred.

Immersion of both legs in hot water (45° C.) produced a definite increase of the blood flow, the maximum being attained after twenty minutes. Simultaneously the buccal temperature decreased and the cutaneous temperature increased. In the height of the vasodilatation thus obtained a deep inspiration was followed by a marked reduction of the blood flow. A loud noise produced the same effect.

Even in basal conditions the plethysmographic method shows that the blood flow to the fingers may be very different from one person to the other. But in the same subject, in different occasions, it is fairly uniform, thus justifying its use for the study of the peripheral circulation.

AUTHORS.

Semisch, C. W. III, and Merves, L.: Electrocardiographic Studies on Artificially Produced Pulmonary Artery Occlusion in Human Beings. *Arch. Int. Med.* 69: 417, 1942.

An electrocardiographic study is presented of fourteen cases of acute pulmonary artery occlusion in human beings incident to partial or complete unilateral pneumonectomy.

The significant changes in the electrocardiographic pattern produced by acute pulmonary artery occlusion in this study are: (1) shift of the electrical axis to the right, 71.4 per cent; (2) development of a deep S wave in Lead I, 50 per cent, and (3) staircase ascent of the RS-T segment in Lead II, 28.6 per cent. These changes tend to appear immediately after the occlusion and to disappear within twenty-four hours, but not constantly so.

The nature of the changes observed are such as to lend support to the belief that electrocardiographic changes associated with pulmonary embolism are produced by strain placed on the right ventricle.

Proper use and interpretation of electrocardiograms, bearing in mind their limitations, may be of help in differentiating pulmonary embolism at its onset from clinically similar diseases.

AUTHORS.

Hall, G. E., Stewart, C. B., and Manning, G. W.: The Electrocardiographic Records of 2,000 R. C. A. F. Aircrew. *Canad. M. A. J.* 46: 226, 1942.

The gross analysis of the electrocardiograms of 2,000 healthy male adults between the ages of 18 and 32 taken while at rest in the recumbent position has

been presented. It is fully appreciated that the value of electrocardiography in diagnosing cardiac conditions is limited. However, the numbers of records showing axis deviation, abnormalities of the T wave in Leads I and II, and the occurrence of prolonged P-R and QRS intervals indicate the value of such recordings at least as an indication for more careful investigation before selection for aircrew duties.

AUTHORS.

Ohnell, v. R. F.: Some Types of Electrocardiograms, Their Relation to Paroxysmal Tachycardia. *Cardiologia* 5: 321, 1941.

Some types of electrocardiograms (with abnormalities between the P and the R wave) have been described and, further, their relation to paroxysmal tachycardia and to the Wolff-Parkinson-White ("WPW") syndrome has been discussed.

Type A.—Gradual rise of the initial part of the QRS complex in one lead. "Conduction-time" subnormal.

Type B.—Gradual rise of the intermediate part between the P wave and the ventricular complex in one lead.

AUTHOR.

Segall, H. N., and Goldbloom, A.: Atrio-Ventricular Nodal Paroxysmal Tachycardia in an Infant Treated With Acetyl Beta Methylcholine. *Canad. M. A. J.* 46: 233, 1942.

Atrioventricular paroxysmal tachycardia in an infant, aged 1 month, was treated with acetyl beta methylcholine. The first dose, 5 mg., administered during the second hour of the attack failed to restore normal rhythm but caused changes in amplitude of QRS and depression of S-T interval. The last dose, 8 mg., produced bradycardia (rate 20 to 56) by slowing abnormal rhythm for about five minutes, then normal rhythm was restored, but there were no changes in QRS and T waves. Adrenalin seems to be preferable to atropine in controlling the disagreeable systemic effects of acetyl beta methylcholine.

AUTHORS.

Kennedy, J. A., and Clark, S. L.: Observations on the Physiological Reactions of the Ductus Arteriosus. *Am. J. Physiol.* 136: 140, 1942.

The authors have established that the ductus arteriosus is a structure which can actively close in response to certain stimuli. It responds to local mechanical stimulation much the same as certain other hollow muscular structures by contracting. The authors do not believe that local mechanical stimulation has an essential role in its closure under physiologic conditions. Neither does a neurologic mechanism appear essential to closure following artificial inflation of the lungs. Their findings are at variance with those of Barcroft, Kennedy, and Mason (1938) with respect to the reaction of the ductus following stimulation of the vagus nerve, but they believe that the present observations have been adequately controlled.

Of the stimuli causing closure of the ductus which the authors have explored, it seems likely that under physiologic conditions breathing is the most important. The actual filling of the lungs by just any gas is not sufficient. From their experiments it appears that oxygen is a necessary component of the gas mixture since inflation of the lungs with pure nitrogen will not cause closure. Oxygen by vein will also cause closure without the necessity of accompanying inflation of the lungs. It is quite possible that many of all of the unexplained closures (see sec. 7) could be due to an increased oxygenation of the fetal blood in response to painful stimulation, struggling of the mother or fetus, hemorrhage, etc. There are other possible sources

of stimulation which the authors have not yet explored fully, such as various natural humoral substances, carbon dioxide, drugs, etc.

Such an influence as that of oxygen on the ductus may have something in common with the findings of Figge (1934), who demonstrated a definite effect on the metamorphosis of the aortic arches and gills in larval forms of the salamander by variations in oxygen tension of their environment.

If this seemingly important relationship of oxygen to the mechanism of closure of the ductus is true, it offers a practical indication for treatment of newborn infants, especially those which have difficulty in the oxygenation of their blood.

AUTHORS.

Castilla, C. R., and Aguirre, R. S.: Congenital Cardiac Block With Stokes-Adams Syndrome With Crises of Paroxysmal Ventricular Tachycardia and Terminal Fibrillation. *Rev. argent. de cardiol.* 8: 340, 1941.

A case is described of congenital auriculoventricular block with syncopal attacks in a boy two and one-half years old. The electrocardiographic study showed that syncopal attacks were due to paroxysmal crises of pre-fibrillation ventricular tachycardia. The boy died of ventricular fibrillation.

AUTHORS.

Wising, P.: Familial, Congenital Sinus Tachycardia. *Acta med. Scandinav.* 108: 299, 1941.

The author gives an account of four cases of permanent sinus tachycardia in two generations of a family in which this abnormality seems to occur as an hereditary anomaly.

AUTHOR.

Wood, P.: Congenital Pulmonary Stenosis With Left Ventricular Enlargement Associated With Atrial Septal Defect. *Brit. Heart J.* 4: 11, 1942.

A case is described which presented the following features: pulmonary valvular stenosis, atrial septal defect, left ventricular dominance, and extreme permanent cyanosis.

The question arises whether this will prove a clinically recognizable congenital syndrome, or whether this is a freak case.

AUTHOR.

Garvin, C. F.: Infarction in Heart Disease. *Am. J. M. Sc.* 203: 473, 1942.

Of 771 consecutive autopsied patients dead of heart disease, 354 (45.9 per cent) had one or more infarcts in the lungs, brain, kidneys, spleen, extremities and/or intestines. Subacute bacterial endocarditis was the type of heart disease most frequently associated with infarcts of the viscera, 80 per cent of the cases showing this complication. In coronary artery disease with myocardial infarction, about 60 per cent of the cases had one or more infarcts in the lungs, brain, kidneys, spleen, extremities and/or intestines. Coronary artery disease without myocardial infarction and rheumatic heart disease were about alike, approximately 50 per cent of the cases showing one or more infarcts. The incidence of infarction in hypertensive heart and syphilitic heart disease was about 40 per cent, and this complication was uncommon in cor pulmonale.

The lungs were involved by infarction in 28.7 per cent of the 771 cases, the kidney in 17 per cent, the spleen in 11.7 per cent, the extremities in 2.6 per cent, and the intestines in 1.7 per cent. There was infarction of the brain in 17.6 per cent of 432 examinations. The highest incidence of infarction occurred in subacute bacterial endocarditis (kidney, 70 per cent; and spleen 66.7 per cent).

The percentage of cases with one organ infarcted was 27.1; with two organs infarcted, 13.5; and with three or more, 5.3. The highest incidence of infarction of multiple viscera was in subacute bacterial endocarditis, 66.6 per cent of the cases having two or more organs infarcted.

AUTHORS.

Kutumbiah, P.: Rheumatism in Childhood and Adolescence. *Indian J. Pediat.* 8: 65, 203, 221, 1941.

The urgency and gravity of the rheumatic problem as it exists in India as yet to be realized by the medical profession and the public at large. Juvenile rheumatism ranks with syphilis, leprosy, and tuberculosis as one of the major problems of national health. In the past four decades much has been done to relieve the sufferings of the victims of leprosy and tuberculosis, by nation wide propaganda and organization. There is a great need for the institution of an active sustained crusade against rheumatic infection following the general principles similar to those successfully being employed against tuberculosis and leprosy. There is at present in existence a nucleus of an organization for controlling rheumatic infection. There are scattered about in the presidency various child welfare centers; in towns and cities there is medical inspection of schools, and in big cities we have adequately equipped and staffed hospitals for the treatment of the diseases of the throat and heart. Most of the work of these existing institutions is inco-ordinated. What is urgently required is to co-ordinate the activities of the existing institutions so that the organized supervision of children both at home and at school may be successfully achieved.

AUTHOR.

McDermott, W., Tompsett, R. R., and Webster, B.: Syphilitic Aortic Insufficiency: The Asymptomatic Phase. *Am. J. M. Sc.* 203: 202, 1942.

Aortic insufficiency due to syphilis is present in a clinically recognizable form for a relatively lengthy period of time (two to ten years) before the development of symptoms.

The asymptomatic form of aortic valvular syphilis is encountered in approximately one-half of the patients with valvular syphilis.

Present-day prognostic data, based as they are on the course following the onset of symptoms of failure, are inapplicable to this large group of patients with cardiovascular syphilis.

There are no available data on the ultimate length of this asymptomatic phase, but it appears from a study of our cases thus far that it can be measured in terms of years rather than months.

AUTHORS.

Pasqualini, R. Q., Lascalea, M. C., and Matera, R. F.: Syphilitic Aortic Valvulitis and Subacute Bacterial Endocarditis. *Rev. argent. de cardiol.* 8: 392, 1942.

A case with necropsy is described of subacute bacterial endocarditis, superimposed on a syphilitic aortitis and valvulitis. Recent studies have shown that this is not a rare association as was formerly thought.

AUTHORS.

Isenhour, C. E., Kuder, K., and Dill, L. V.: The Effect of Parity on the Average Blood Pressure and on the Incidence of Hypertension. *Am. J. M. Sc.* 203: 333, 1942.

No demonstrable difference can be noted in the incidence of hypertension and the average blood pressure levels of parous and nulliparous women.

It seems likely that the hypertension and hypertension-producing diseases which occur following a large portion of the "toxemias of pregnancy" are not the result

of this complication of pregnancy, but rather that this complication of pregnancy occurs for the most part, if not exclusively, in patients whose vascular systems are endowed with the tendency toward hypertensive disease.

AUTHORS.

McLennan, C. E., McLennan, M. T., and Landis, E. M.: The Effect of External Pressure on the Vascular Volume of the Forearm and Its Relation to Capillary Blood Pressure and Venous Pressure. *J. Clin. Investigation* 21: 319, 1942.

The pressure plethysmograph was used to determine the effect of graded external pressure on the vascular volume of the forearm, for the purpose of determining the usefulness of this procedure in estimating the blood pressure in the minute vessels collectively.

With external pressures ranging from 0 to 90 mm. Hg, pressure-volume curves were determined in twenty normal subjects (a) by suddenly arresting the circulation to the forearm and measuring decrease in volume during the ensuing mild hyperemia. The term "dynamic vascular volume" was used to indicate that the volume of blood in actual movement was being measured under these conditions.

In the normal forearm "dynamic vascular volumes" were greatest when external pressure was between 15 and 35 mm. Hg, becoming less at external pressures above and below this range.

To record the relation between "dynamic vascular volume" and external pressure in the form of a single numerical value, an objective method of analyzing the pressure-volume curves was adopted. The single value thus obtained was termed P_{mve} and was defined as "that external pressure at which the vis a tergo of the circulation is able to keep open the greatest collective dynamic vascular volume."

P_{mve} determined in the forearms of twenty normal subjects with the forearm segment at heart level and at 34° C. was 27, 21 and 21 mm. Hg by Methods I, II, and III respectively. Reasons are given for regarding Methods I and II as the most useful. In the normal subject the results by all three methods had roughly the same order of magnitude as average capillary blood pressure when determined directly.

This similarity between P_{mve} and directly determined capillary blood pressure held also when the latter was reduced by elevating the forearm or increased by known venous congestion and by depressing the forearm below heart level.

With due precaution against assuming too quickly the quantitative validity of any indirect method of measuring intravascular pressure, it is suggested that the plethysmographic method may be useful in studying the volume of blood and the pressure in the minute vessels of the forearm in clinical conditions.

AUTHORS.

Flaxman, Nathan: Hypertensive Heart Disease of 10 to 20 Years' Duration; Report of 11 Cases. *Ann. Internal Med.* 15: 821, 1941.

Eleven cases of hypertensive heart disease in patients who lived ten to twenty years (average 13.7 years) after the onset of the first cardiac symptoms are reported. They were of all ages from 25 to 70 years and had various cardiac rhythmic and conduction disturbances, neither factor apparently influencing the longevity.

AUTHOR.

Richards, D. W., Jr., Cournand, A., Darling, R. C., Gillespie, W. H., and Baldwin, E. DeF.: Pressure of Blood in the Right Auricle in Animals and in Man: Under Normal Conditions and in Right Heart Failure. *Am. J. Physiol.* 136: 115, 1942.

In the study of venous pressures in one chimpanzee and a series of dogs, the development of right heart failure associated with acute pulmonary edema was accompanied not only by rise of peripheral and right auricular pressures, but also

by a disappearance of the normal pressure gradient between peripheral veins and right heart, the right auricular and peripheral venous pressure levels becoming nearly equal.

In nine human subjects with apparently normal circulations, right auricular pressure was recorded directly by means of right heart catheterization. The average gradient from arm to heart was +41 mm. of water. In six subjects absolute pressure levels at the right auricle were determined by locating the position of the catheter by lateral x-ray; the average right auricular pressure (subjects supine) was +37 mm.

Three patients in congestive heart failure, with high peripheral venous pressures, showed decrease in peripheral-central pressure gradients, the pressures in arm vein and in right auricle being almost identical.

AUTHORS.

Hardy, A. G., and Denham, H. E. H.: Popliteal Aneurysm. Report of a Bilateral Case Treated by Bilateral Excision. Guy's Hosp. Rep. 90: 244, 1941.

A case of bilateral popliteal aneurysm is described. Methods of investigating the condition of the aneurysm and, more particularly the collateral circulation of the limb, are discussed.

On one side spontaneous thrombosis had occurred with intensification of symptoms. Excision of the aneurysm under local anesthesia was followed by uneventful recovery, presumably due to establishment of an adequate collateral circulation. Excision of the aneurysm on the opposite side was followed by threatened gangrene which was only narrowly averted.

The various forms of alternative operations are discussed and the arguments in favor of the modern treatment by excision of the aneurysm are put forward.

We have been unable to find a report in the literature of any other case of successful bilateral resection of a popliteal aneurysm.

AUTHORS.

Keen, J. A.: The Collateral Venous Circulation in a Case of Thrombosis of the Inferior Vena Cava, and Its Embryological Interpretation. Brit. J. Surg. 29: 105, 1941.

A rare case of thrombosis of the inferior vena cava with fibrous tissue formation and calcification is described, together with x-ray findings and accounts of the microscopic sections of the thrombosed vessel and of the kidney showing the perinephric venous circulation. The collateral circulation which became established in the posterior abdominal wall is traced and illustrated. The literature on the development of the inferior vena cava is reviewed, and this is followed by an embryologic explanation of the collateral circulation on the basis of a simplified ground plan.

AUTHOR.

Price, P. B., Sloan, H. E., Jr., and LaRochelle, F. T.: A Study of Mechanical Factors in the Circulation, With Spécial Reference to the Problem of Acute Circulatory Failure. Bull. Johns Hopkins Hosp. 52: 26, 1942.

Many features of the normal blood circulation have been reproduced in a mechanical circulation model, and certain changes which characterize acute circulatory failure have been studied experimentally in the machine and in dogs. The behavior of the machine under controlled conditions provides a number of suggestive clues to the complex problem of hemodynamics. The general impression received by the authors is that the living circulation is influenced by mechanical factors to a degree not generally appreciated heretofore.

The mechanical circulation is essentially a series of fluid-filled, pressure reservoirs in dynamic equilibrium. When this balance is upset by external factors, the machine

tends automatically to establish a new equilibrium by redistributing its circulating fluid between the different vascular compartments. It is suggested that under analogous conditions similar adjustments take place in the animal.

On the basis of this study the following statements are believed to express general principles in hemodynamics: blood pressure has a definite relationship to the elasticity and distension of the vascular system; changes in peripheral resistance tend to have opposite effects upon arterial pressure and cardiac output; effects of postural changes upon regional and general blood flow depend upon the degree of dilatation or collapse of blood vessels produced by the variations in hydrostatic pressure, as well as upon the efficiency of venous valves and the pumping action of respiration and other muscular movements; peripheral resistance varies with velocity of flow, viscosity of blood, and size of blood channels.

The view that acute circulatory failure, such as occurs in shock, may be due to a disparity between blood volume and vascular capacity is criticized.

The concept of a minimum effective blood volume is introduced, and reasons are suggested why comparable persons vary so greatly in blood volume, in susceptibility to blood loss, and in response to blood transfusion.

AUTHORS.

McIntosh, R.: Circulatory Failure in Acute Glomerulonephritis. *Canad. M. A. J.* 46: 445, 1942.

One of the clinical features of acute glomerulonephritis, namely, the accompanying picture of circulatory failure, is discussed. Although its presence is in no sense difficult to recognize when the symptoms and signs are well marked, the frequency of its occurrence in relatively mild degree has only recently come to be appreciated, and the question is fairly raised whether it is always given due weight in the evaluation of a given clinical situation. Because of its importance in determining the outcome in some of the cases of acute nephritis which prove fatal early in the attack, the necessity of sparing the heart any unwarranted burden should be borne in mind in all cases—even the mildest ones.

AUTHOR.

Ane, J. N., and Burch, George E.: Effects of Roentgen Irradiation Upon Linear Rate of Flow in Cutaneous Lymphatics of Humans. *Proc. Soc. Exper. Biol. & Med.* 48: 471, 1941.

Data obtained from seven human beings indicated that small doses of roentgen irradiation (220-450 r) to the skin are not likely to disturb the linear flow of lymph in the cutaneous lymphatics, while large doses sufficient to produce a first degree skin reaction probably will reduce the rate of lymph flow.

AUTHORS.

King, A. B.: Demonstration of the Basilar Artery and Its Branches With Thorotrast. *Bull. Johns Hopkins Hosp.* 52: 81, 1942.

The basilar artery and its branches were successfully demonstrated in a living human subject by means of thorotrast. There were no untoward reactions. The procedure should be considered in patients when the differential diagnosis includes aneurysms or defects of these vessels.

AUTHOR.

Brock, R. C.: Experiences in Pulmonary Artery Ligation. *Guy's Hosp. Rep.* 90: 217, 1941.

The historical development of pulmonary artery ligation is mentioned; the first deliberate dissection of the main vessels was by Rienhoff in July, 1933. The opera-

tive approach is discussed and the posterolateral incision recommended; an anterior approach does not give room enough to make the necessary manipulations with full freedom and safety.

Infiltration of the hilum with local anesthetic is advised in order to diminish harmful stimuli and to facilitate dissection. A description of the operation in the two sides is given; the exposure on the left side is much easier than on the right.

The exposure of the right pulmonary artery is made much easier by recognition of a constant triangular facial fold passing from behind the lowest part of the superior vena cava across the front of the right pulmonary artery. This fold can be divided with impunity. Its division both frees the vena cava for retraction medially and exposes the stem of the right pulmonary artery. This triangular bloodless fold has not been described or deputed before.

Mention is made of direct estimation of the pulmonary blood pressure in man. Direct estimation before and after ligation shows no change in the arterial pressure demonstrating that compensation is immediate and that simple back pressure on the heart is not the cause of death or grave illness in pulmonary embolism. This is an original observation in man.

The effects of ligature of the right or left pulmonary artery without removal of the lung are discussed; sloughing is prevented by the bronchial arteries.

In the eighteen cases in which pulmonary artery ligation was performed no direct ill effect could be attributed (except for one in which death followed a slipped ligature). The tying of the artery produces no observable clinical effect; the pulse rate remains unaltered and neither the pulmonary nor the systemic blood pressure changes. In the last twelve cases accompanied by pneumonectomy, only two deaths occurred and these were both three weeks after operation; in one case from a lung abscess, in the other from pericarditis. The ability of the cardiovascular system to accommodate itself rapidly to the profound changes caused by sudden shutting off of one-half of the pulmonary arterial system is thus amply proved.

AUTHOR.

Wiggers, H. C., Duschatko, A. M., and Kory, R. C.: The Circulatory Response of the Unanesthetized Dog to Small Physiological Quantities of Adrenalin. *Am. J. Physiol.* 136: 87, 1942.

It appears that the unanesthetized dog will exhibit either an elevation or a depression of blood pressure in response to small intravenous injections of adrenalin, the direction depending upon the dose per unit of animal weight. The depressor reaction, which can be uniformly elicited by 0.1 $\mu\text{g.}/\text{kg.}$ per kilogram quantities, is reproducible in the same dog at twenty-minute intervals. Shorter intervals were not investigated. Slightly stronger concentrations of this drug may elicit either pressor or depressor effects, the latter being slightly more prevalent. Although the factors which govern the direction of the response are not completely understood, it is suspected that the initial emotional status of the animal is of considerable importance. The rate of injection does not appear to influence the direction of the response.

Since the depressor response is characterized by a predominant reduction of systolic pressure, it becomes increasingly difficult to accept the doctrine that a diminution of systemic peripheral resistance is the precipitant mechanism. We are more inclined to postulate an initial dilatation of pulmonary vessels with a consequent reduction of pulmonary arterial resistance and thus a temporary pooling of blood within the lung vessels. Hence, a transient reduction of left ventricular filling will ensue which will be further accentuated by the simultaneous tachycardia.

It has also been suggested that adrenalin may augment the capacity of the aorta and its immediate large branches. This would also exert directional effects upon the pulse pressure pattern similar to those resulting from a reduced stroke volume of the

left ventricle. These two mechanisms may even act synergically in bringing about the adrenalin depression of arterial blood pressure.

AUTHORS.

Gootnick, A., Saland, G., Klein, C., and Zurrow, H.: Studies on Vasodilatation Tests in Peripheral Vascular Disease. *J. Lab. & Clin. Med.* 27: 878, 1942.

In the study of the patient who presents himself with symptoms referable to the peripheral arterial tree, all three tests discussed have a place. The place for each is indicated in the results the authors have summarized in the accompanying tables.

Sodium nitrite injected intravenously and the hot water bath are both useful as preliminary tests for vasospasm. Of the two, the thermal test is better suited to patients with vascular involvement when we wish to discover the degree of associated vessel spasm. In patients who give the clinical impression of nonorganic vasopastic involvement the nitrite test is considerably more dependable. It is also feasible for patients prone to syncope in a hot bath.

In this clinic a patient whose vasodilatation in response to either of these tests reaches normal values is then regarded as possessing normal vascular reserve. Those who respond to either of these tests with subnormal vasodilatation are then tested with peripheral nerve block. The advantage of this scheme is that in a considerable proportion of patients a simple, nonmanipulative procedure serves adequately to reveal the intensity of spasm and the vascular reserve of the limb in question. Nerve block is reserved as the test of last appeal for those patients in whom either the thermal stimulus or the sodium nitrite failed to induce fully normal vasodilatation.

AUTHORS.

Spealman, C. R.: The Action of Ions on the Mammalian Heart. *Am. J. Physiol.* 136: 332, 1942.

In the guinea pig right atrium preparation, certain depressive or abnormal changes, such as a decrease in rate which was usually progressive, a depression of the amplitude of contraction, or arrhythmia, occurred when the concentration of the various ions was too different from normal. Within limits close to normal, the most definite positive effect was the variation of the amplitude of contraction with the Ca ion concentration. There was also some suggestion that increasing the Ca ion concentration caused an increase in the duration of the response, while increasing the K ion concentration caused a decrease in the duration of the response.

In the Langendorff preparation of the guinea pig heart, the heart rate was independent of the K ion and Ca ion concentrations within regions close to normal, but was depressed in certain instances where the concentration was too different from normal. The P-R interval lengthened as the Ca ion concentration increased, and shortened as the K ion concentration increased. The Q-T interval was lengthened as the Ca ion concentration decreased, but was not greatly affected by changing the K ion concentration.

In the acute experiments on dogs, in which the plasma Ca concentration was varied, the intraventricular pressure, the P-R interval, and the height of the P wave all tended to vary in the same sense with the plasma Ca concentration. The duration of response was slightly decreased and the heart rate was increased when the plasma Ca concentration was raised. The Q-T interval, the height of the R wave, and the height of the T wave showed no very definite tendencies to vary with the plasma Ca concentration.

In the acute experiments on dogs in which the plasma K concentration was varied, the intraventricular pressure and the height of the T wave tended to vary in the same sense and the P-R interval in the opposite sense with the plasma K concentration. The magnitude of the intraventricular pressure changes was small. The duration of response was slightly decreased when the plasma K concentration was raised. The

heart rate, the Q-T interval, the height of the P wave, and the height of the R wave showed no definite tendencies to vary with the plasma K concentration.

AUTHOR.

Zwemer, R. L., and Arrighi, F. P.: Modification of the Activity of the Heart of the Frog Produced by Chloride of Potassium. *Rev. argent. de cardiol.* 8: 301, 1941.

Toads injected intraperitoneally with a lethal dose (1 c.c. per 100 Gm. weight) of a 10 per cent solution of potassium chloride and with a nonlethal dose (1 c.c. per 100 Gm. weight) of a 6 per cent solution, develop important cardiac alterations which are permanent in the former and transient in the latter. The following observations were made:

1. The activity of the sinus is depressed and bradycardia is observed.
2. The activation of the myocardium is slow as shown by broadening of P-R and B waves.
3. The excitability of the heart decreases as shown by an increase of rheo base and chronaxie.
4. Other alterations in the activation of the myocardium manifest themselves by variations in the order of activation of the chambers of the heart, irregularities of P and R, appearance of an S wave, ventricular fibrillation, electrical alternation, extrasystoles, etc.
5. The recovery phase of each beat is disturbed because T becomes irregular diphasic or negative.
6. These cardiac alterations are fairly parallel to the general disturbance (asthenia, loss of reflexes) and the toads injected with nonlethal dose of potassium chloride recover the normal cardiac and general state.

AUTHORS.

Flaxman, N.: Clinical Value of Digitalis in Hypertensive Heart Failure. I. With a Normal Rate and a Regular Rhythm. *Am. J. M. Sc.* 203: 741, 1942.

The study of 160 cases of hypertensive heart failure with a normal rate and a regular rhythm is reported.

The age of the patient and the duration of the symptoms before treatment with digitalis apparently had no influence on the outcome.

Of all the hypertensive patients who develop congestive heart failure, those with isolated failure of the left ventricle, a normal heart rate, and a regular rhythm have the best prognosis.

Factors over which digitalis itself had no control, such as uremia, coronary thrombosis, and cerebral hemorrhage, caused twenty-two (64 per cent) of the thirty-seven deaths in this series of 160 cases.

Treatment with digitalis may be regarded as most successful in these decompensated hypertensive patients, despite the normal rate and the regular rhythm.

AUTHOR.

Corrigendum

In the May, 1942, issue of the JOURNAL, Vol. 23, page 636, the discussion of Dr. William S. Collens should have read as follows:

I should like to congratulate the authors and wish to say that Dr. Boas and I recently conducted the same kind of studies and came to the same conclusions. We used the apparatus which we devised for intermittent venous occlusion, and modified it by attaching four cuffs. Three cuffs were inflated at one time while one cuff was deflated in sequence.

Book Review

ESSENTIALS OF ELECTROCARDIOGRAPHY: By Richard Ashman, Ph.D., Professor of Physiology, and Edgar Hull, M.D., Professor of Medicine, Louisiana State University Medical Center. The Macmillan Company, New York, 1941, ed. 2, 373 pages, 122 illustrations, \$5.00.

Like many other developments in medicine, the practical application of electrocardiography has outrun our knowledge of some of its fundamental concepts. Every student of the subject is tortured by dissatisfaction with his grasp of these fundamental facts. Worse still, many of us who are lacking in adequate discipline in the sciences of mathematics and electricity are scarcely able to comprehend reports of research in electrocardiography whose basis implies an understanding of those sciences. This text represents a unique attempt to express essential researches bearing on fundamental electrophysiologic concepts underlying this subject in terms that are comprehensible to any earnest student. The first seventy-five pages are devoted to this, but, throughout the text, in the consideration of various electrocardiographic phenomena, explanations are given which refer the reader to these basic concepts. If nothing more than this had been done, it would justify bringing out a second edition of this book. However, the discussion of fundamentals would gain in clarity and would be more widely comprehended if greater use of diagrams had been made.

The next section of the book considers the components of the auricular and ventricular complexes. These are treated in the order of their occurrence, normal characteristics are described, limits of normal variation indicated, and changes produced by disease are stated. Two chapters deal with disturbances of the cardiac mechanism.

The remainder of the book deals with the electrocardiogram in diseases of the heart. This discussion is well organized and is of great practical importance. However, some subjects suffer from too brief a treatment. In other instances, more electrocardiograms to indicate variations within a given pattern would have been desirable for greater clarity.

The reviewer would take mild exception to such statements as, "The recognition of early and relatively mild changes in the myocardium may be, we believe, greatly facilitated if the electrocardiographer pays more attention to minor deviations from normal." This is "heady medicine," and tends to encourage those who make too much of too little in the interpretation of electrocardiograms. Anyone who fathers a book on this subject is chagrined more by those who see too much in a tracing than by those who see too little. More emphasis on the unreliability of the electrocardiogram as a means of excluding the possibility of coronary sclerosis or of establishing such a diagnosis unless previous acute myocardial infarction had occurred would have served a useful purpose, in my opinion.

Despite these minor criticisms this book deserves a wide circulation. It is clearly written and generally sound, and will furnish safe guidance for the student and practitioner; no one can read its chapters on the fundamental basis of electrocardiography without a feeling of gratitude to the authors.

A. R. BARNES.

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*Executive Committee.

American Heart Journal

VOL. 24

SEPTEMBER, 1942

No. 3

Original Communications

CHANGES IN THE SIZE OF THE HEART IN CHILDREN WITH RHEUMATIC FEVER

JOHN D. KEITH, M.D., AND MIRIAM BRICK, M.D.
TORONTO, CANADA

REFERRING to roentgenograms of the heart, White¹ points out: "There are so many factors, for example, age, size, build, respirations and nervousness, resulting in individual variations within the normal that it is at present impossible to recognize them all or at least to take them into consideration in the establishment of any satisfactory tables of measurement of normal size. . . . Successive records of heart size and shape in the same individual are more useful than a single comparison of this individual case with a table of normal averages or a set of rules."

Our purpose in this study has been to compare successive roentgenograms, taken at different times on the same patient. In this way the various interfering factors of a constant type are diminished or eliminated. However, there are two sources of error that should be referred to in evaluating roentgenograms of the heart in the same patient. One is the effect of respiration on the shape of the heart shadow, and the other is that of systole and diastole. The latter is slight, and, in older children, a long enough roentgenographic exposure will overcome it. The former factor we attempted to eliminate by catching the patient in the same respiratory phase each time, i.e., the neutral phase. These sources of error obviously have not been ruled out completely, but we believe they have not been sufficient to interfere with the general conclusions which we reached.

From the wards and laboratories of the Hospital for Sick Children, Toronto, and the Department of Paediatrics, University of Toronto, under the direction of Alan Brown, M.D., F.R.C.P. (London).

Read at the Eighteenth Annual Meeting of the Canadian Society for the Study of Diseases of Children, Brockville, Ontario, June 14, 1941.

Received for publication Jan. 11, 1942.

Roentgenograms were taken with the patient standing and the plate 7 feet from the tube. Three standard positions were used: (1) postero-anterior; (2) left anterior oblique, with the patient at an angle of 50° ; and (3) right anterior oblique with the patient at an angle of 55° while a swallow of barium was being administered. The posteroanterior position was used in all cases; the other two positions were utilized routinely at first, but latterly only when they appeared to be indicated in more severe cases. The left anterior oblique at 50° was chosen because of the contention of Wilson² that at this particular angle the shadow of the heart just clears the vertebral column in the normal subject.

Measurements were obtained from the roentgenograms in the posteroanterior position (P.A.). These included the transverse diameter of the heart (T.D.), the internal diameter of the chest (I.D.), and the cardiac surface area (C.S.A.), estimated by a Diezten planimeter. The body surface area (B.S.A.) was obtained by means of a Du Bois chart from the height and weight.

These results were tabulated for each case, as shown in Table I.

TABLE I

Admitted 6/24/39. Dismissed 10/31/39. First attack of rheu- matic fever. Mitral systolic murmur which disappeared after six months. Al- lowed up 9/1/39	DATE	HT.	WT. (LB.)	B.S.A.	T.D.	I.D.	C.S.A.	B.S.A. C.S.A.	NORMAL C.S.A.
	6/29/39	5'	103	1.4	15.2	24.0	159	8.7	77-84
	7/18/39	5'	103	1.4	12.5	22.9	104	13.4	77-84
	8/ 3/39	5'	103	1.4	11.5	23.6	92	15.1	77-84
	9/14/39	5'	103	1.4	11.4	24.0	95	14.6	77-84
	10/25/39	5'	106	1.42	11.2	23.2	90	14.9	77-84
	2/16/40	5'1"	117	1.5	11.5	23.9	82	18.2	77-84

In a preliminary study of the question of change in the size of the heart, two particular points were noted with regard to normal hearts that appeared to bear on this problem. The first was the effect of rest in bed on the size of the heart, and the second the effect of heart rate on enlargement of the heart.

Roentgenograms were taken of the hearts of seven surgical patients who had been in bed for four to six months. The ratio of the transverse diameter of the heart to the internal diameter of the chest in these cases varied from 40 to 45 per cent, i.e., all were slightly smaller than the average standard for their height. However, normal standards are difficult to evaluate and further evidence was sought. At this time a patient who had been kept in bed for a year because of a minor abnormality in the electrocardiogram was referred to the hospital. The heart showed no pathologic abnormalities, and the patient was allowed up gradually with no ill effects. Six months later she was well and active and the heart was normal. Roentgenograms of the heart were taken just before she began to get up, after she had been up for two months, and after she had been up six months. These are shown

in Fig. 1*A*, *B*, and *C*. In Fig. 1*A* the heart is obviously small. In Fig. 1*B* it is a little larger, and in Fig. 1*C*, larger again. But even in Fig. 1*C* it is still a little smaller than the average for her height and weight. It was concluded that her heart was smaller than normal because of the bed rest for one year. Since then many other cases have come to our attention, and whenever prolonged rest in bed has occurred (a year or more) the heart appears considerably smaller than normal.

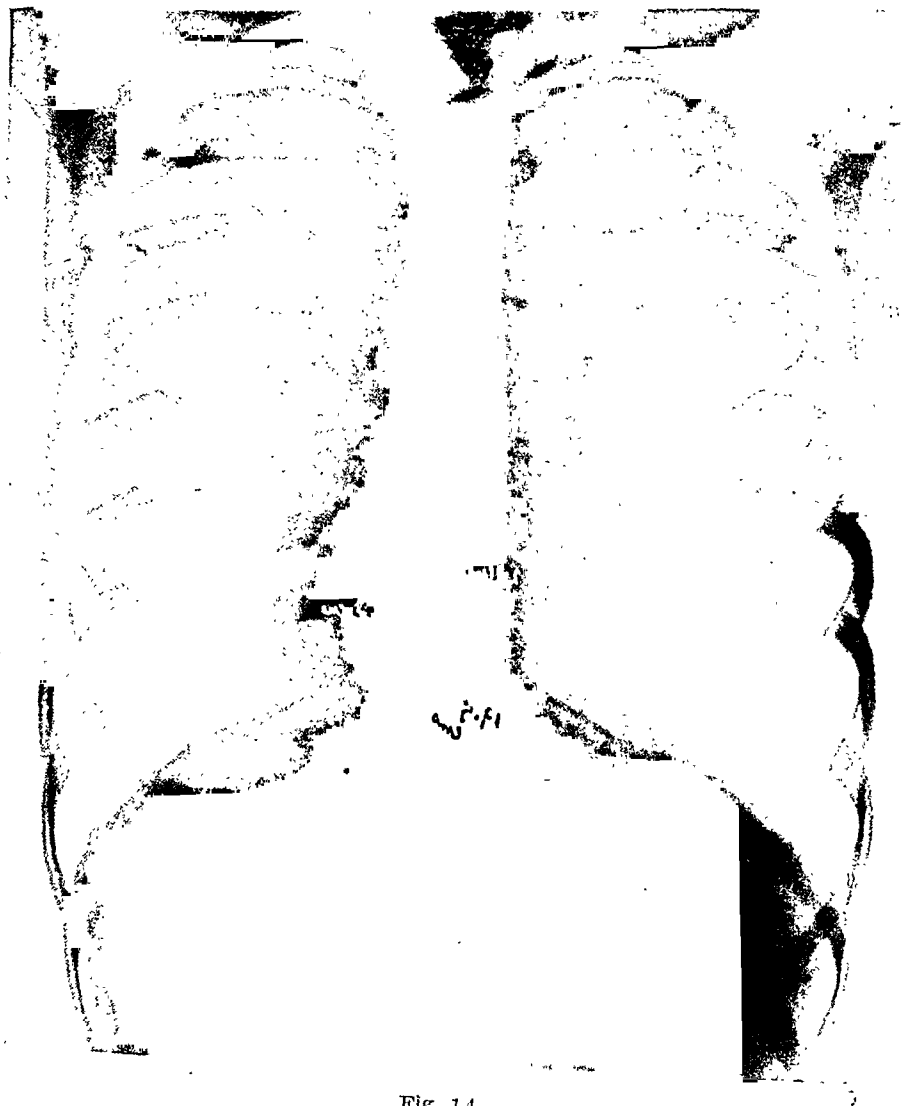


Fig. 1*A*.

Fig. 1.—H. S. had been in bed for one year with normal heart. *A*. Before getting up; *B*, after being up two months; *C*, after being up six months.

The effect of heart rate on the size of the heart was noted in three categories: (1) bradycardia, (2) moderate tachycardia, and (3) paroxysmal tachycardia over 200. Bradycardia was found to produce a slight, but definite, enlargement in a patient with heart block and no

other cardiac defects (see Fig. 2A). Moderate tachycardia was found to produce no change in size, even with rates up to 180 or 200 beats per minute.

An interesting case to compare with the one of bradycardia is that of a 12-year-old child who spent two years in bed with hyperthyroidism and a tachycardia of 140 beats per minute continuously (Fig. 2B). There was no evidence of heart disease, and a roentgenogram of the heart showed that it was a great deal smaller than normal.

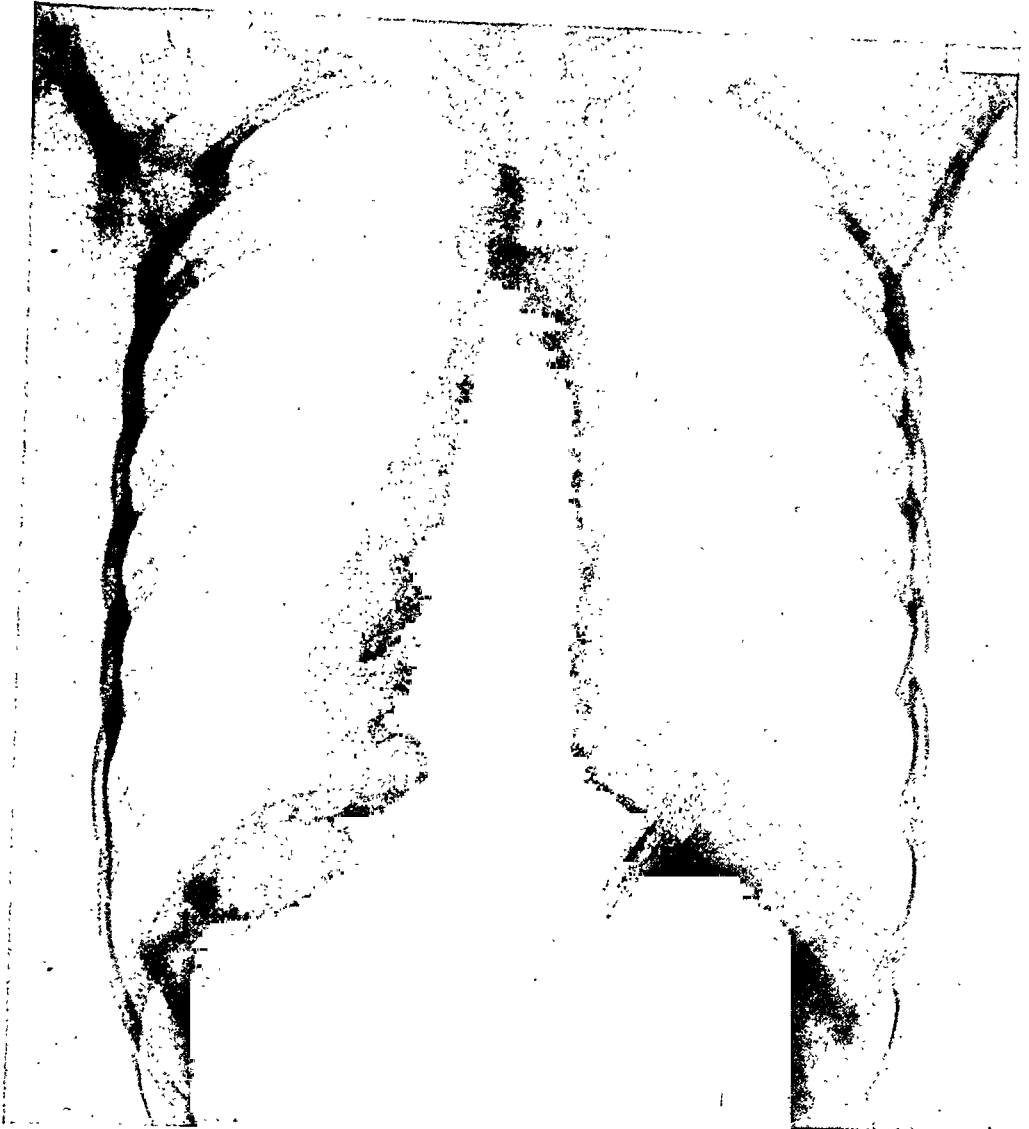


Fig. 1B.

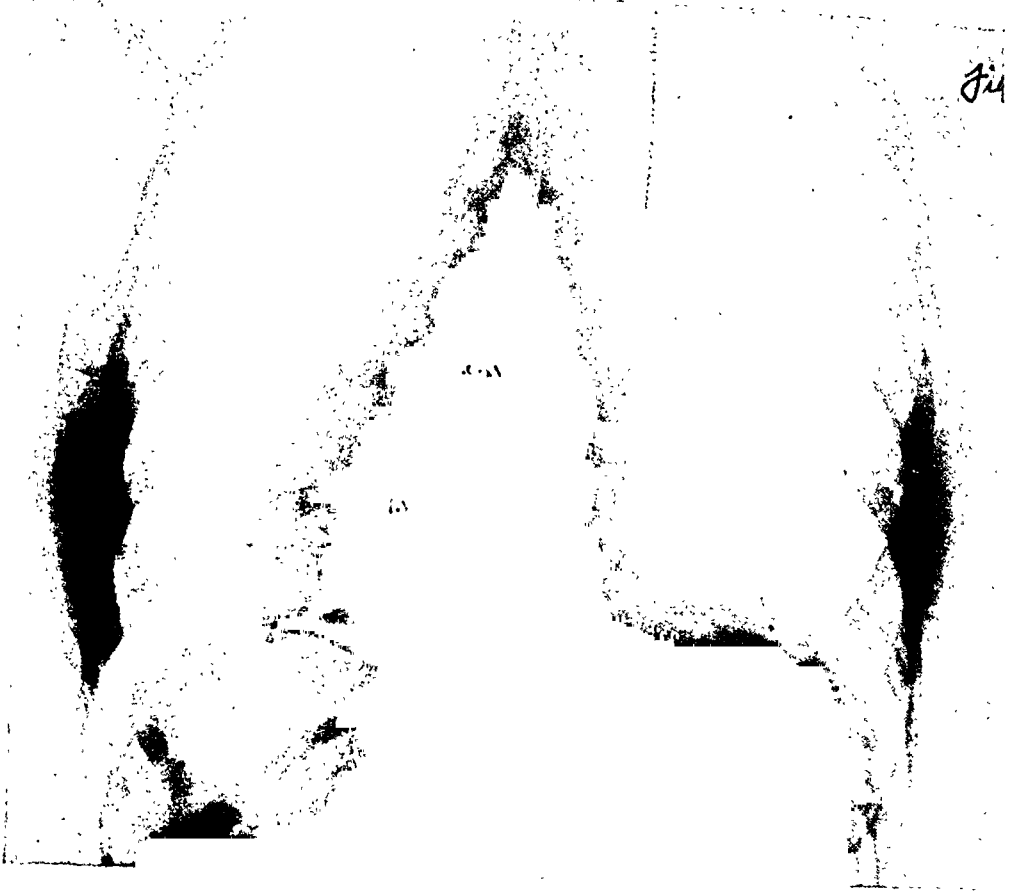
In a case of moderate paroxysmal tachycardia reported by Keith and Brown,³ there was the same lack of effect of tachycardia on the size of the heart. An increase in heart rate, even approaching 200 beats per minute, does not appear to produce enlargement unless it is accompanied by some cardiac lesion.

When the rate is over 200 the effect is variable. Most patients show no enlargement immediately, many do in a few days, and nearly all do if the rate persists at such a high level for one to two weeks or more, particularly if signs of failure have begun to appear. An illustrative case is the following: J. E., 13 years of age, has one or two attacks of paroxysmal tachycardia a year. Roentgenograms of the heart, taken at the time of an attack, have been described in detail in



Fig. 1C.

a previous publication.³ The roentgenograms are shown in Fig. 3A, B, and C. The importance of this case lies in the fact that the patient had rapid dilatation of the heart with no disease of the myocardium, and that rapid dilatation may occur within three days and disappear in a week. This leads one to wonder whether such rapid dilatation of the heart can occur when no disease is present, and then, if the myo-



A.



B.

Fig. 2.—B, S. H., tachycardia of 140 for two years (hyperthyroidism); A, M. D., bradycardia, rate 40 to 50 (heart block).

cardium is affected, as in severe rheumatic fever, whether the same degree of rapid enlargement will develop with the heart beating at a considerably slower rate.

With these points in mind we wished to ascertain how much enlargement of the heart takes place during a single attack of rheumatic fever, and how much smaller the heart may become as the attack subsides.

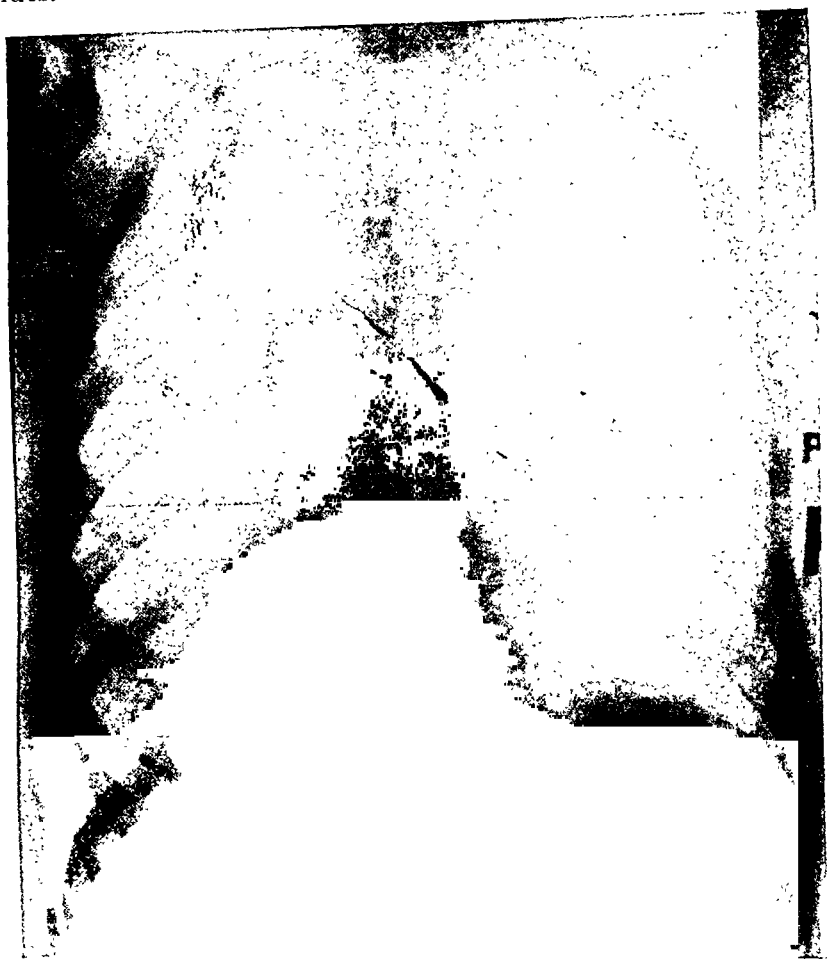


Fig. 3A.

Fig. 3.—J. E., A, Normal heart size; B, after three days of heart rate over 200; C, after two weeks of heart rate over 200.

RESULTS

One hundred patients with rheumatic fever were studied roentgenologically during the various stages of a single attack of the disease. From two to twelve roentgenograms were taken on each patient, the average being four. Ninety-six of the 100 had either rheumatic myocarditis, endocarditis, or pericarditis, and four had doubtful signs of

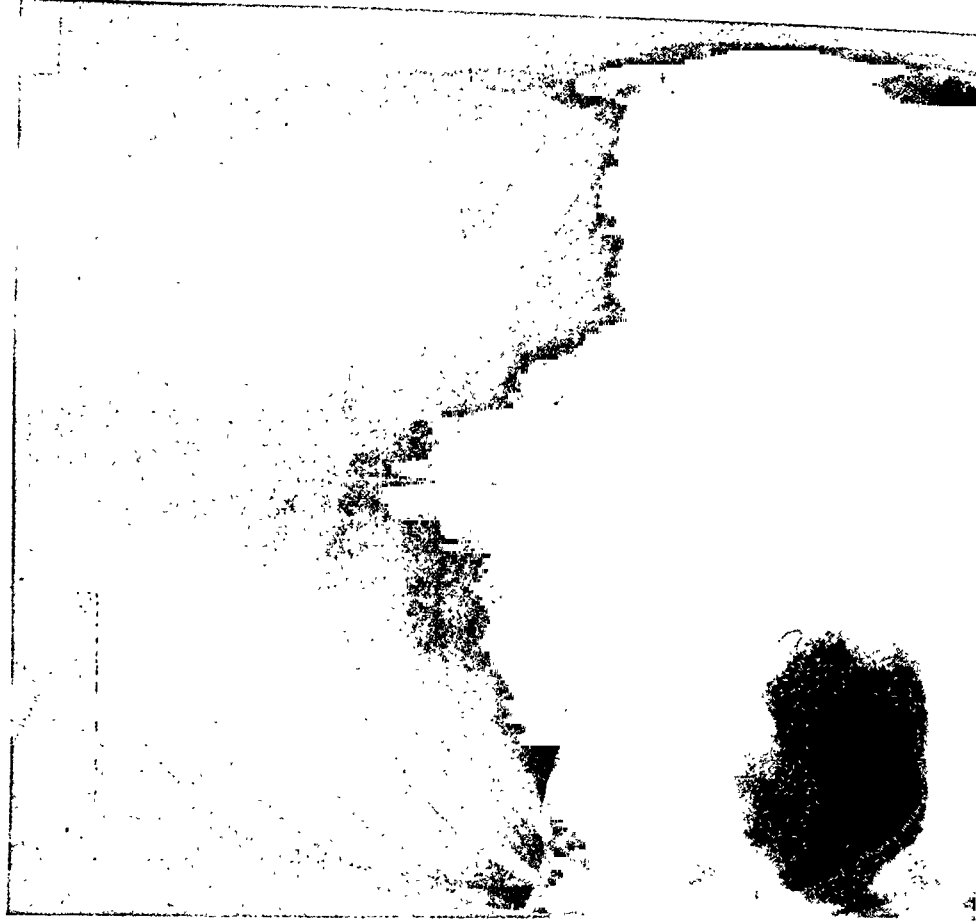


Fig. 3C.

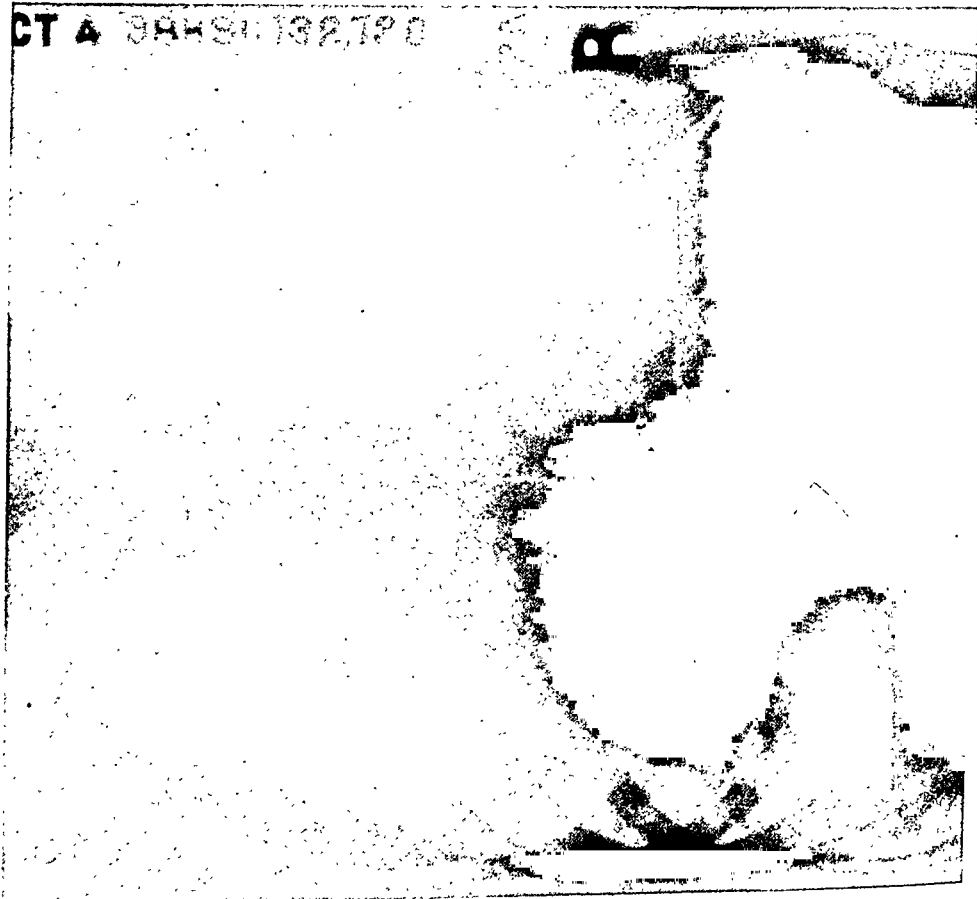


Fig. 3B.

heart involvement. The cardiac surface area on admission was compared with the cardiac surface area when progressive change had ceased to occur; that is, the figure set down as representing the alteration in the size of the heart refers to the greatest change during the attack, regardless of whether the heart was getting larger or smaller. This change in size has been set down for each individual case and recorded in chart form (Chart 1).

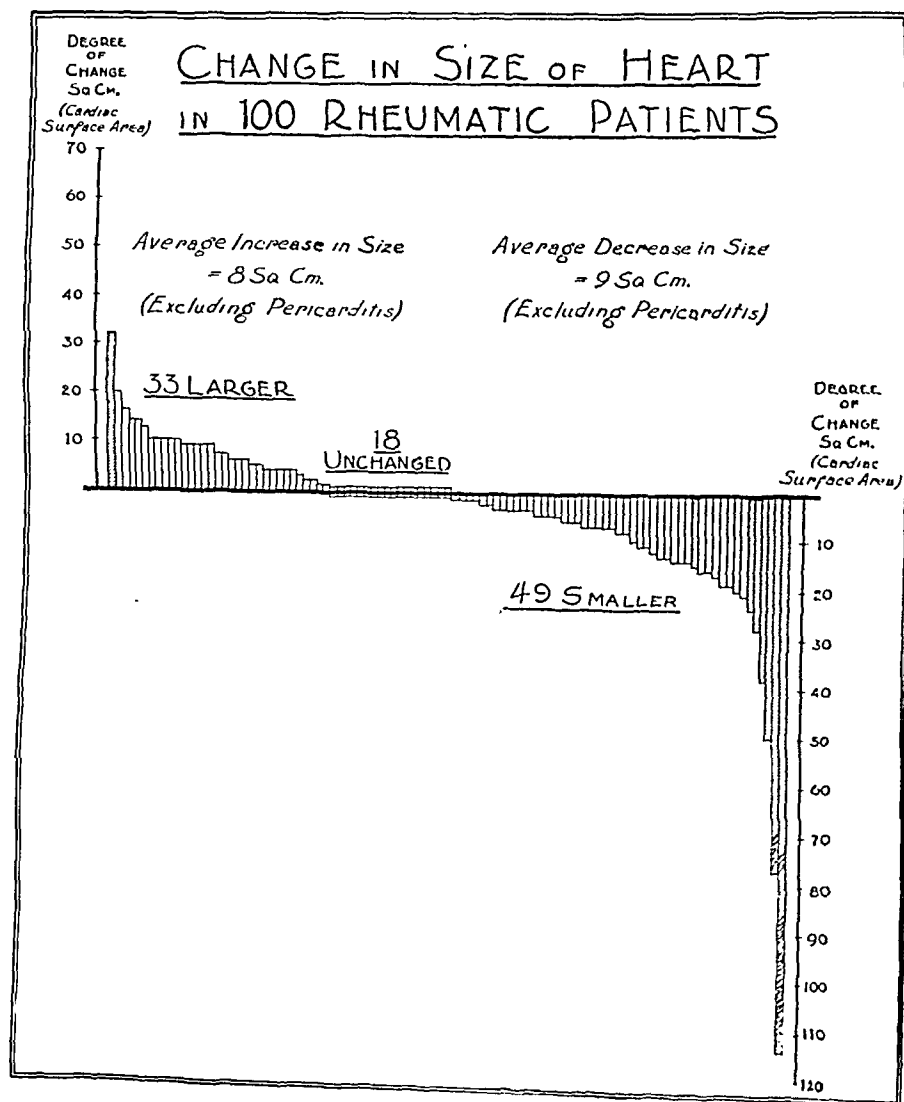


Chart I.

It will be noted that thirty-three of the hearts became larger, eighteen remained unchanged, and forty-nine became smaller. Cross hatching indicates pericarditis with effusion, and it will be seen that this produced the greatest change in the size of the heart shadow. Half of

the hearts became smaller, and a quarter remained unchanged or became only slightly larger. The general outlook in a single attack is relatively good, therefore, although it must be remembered we were unable to include patients who were too ill to be roentgenographed on admission to hospital. Leaving out the cases of pericarditis, the average increase was approximately the same as the average decrease, i.e., 8 sq. cm. as compared with 9 sq. cm. The time required for this change

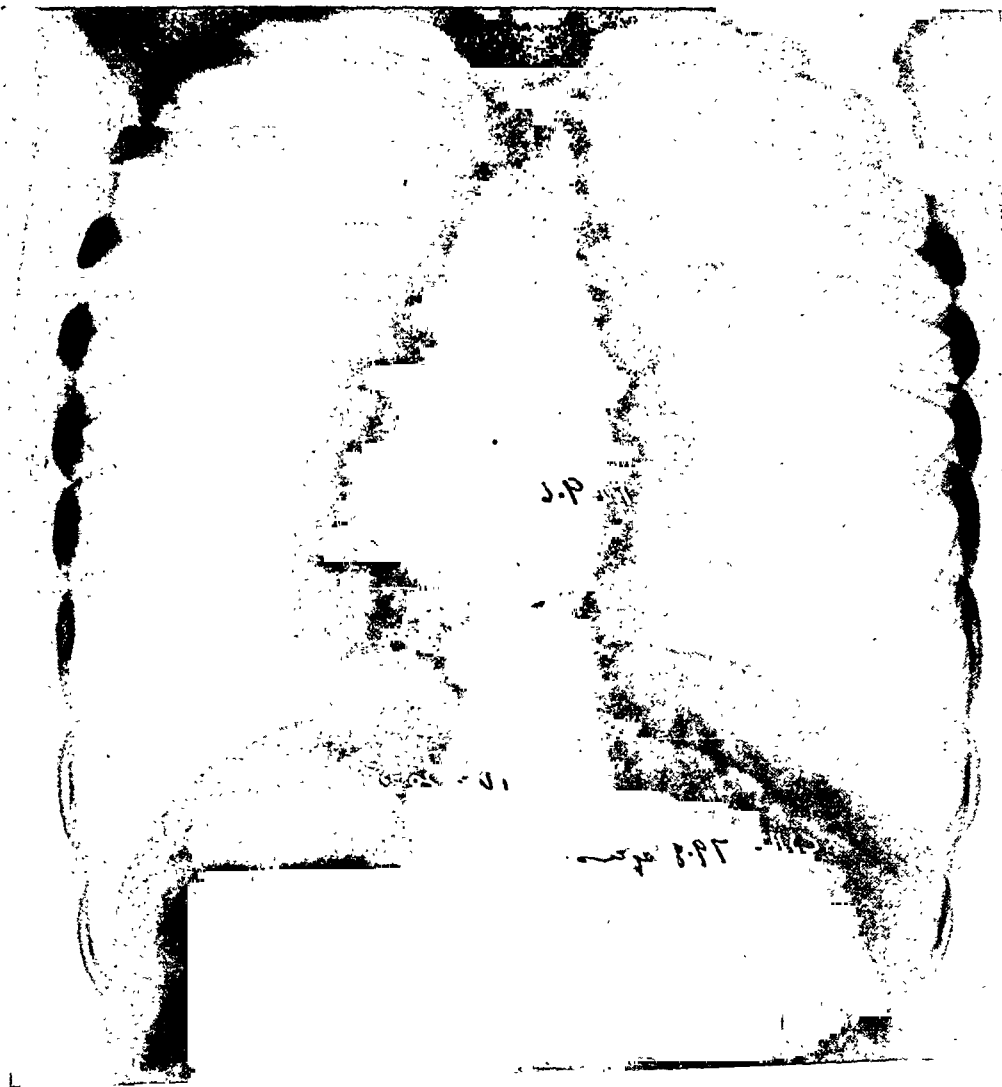


Fig. 4A.

Fig. 4.—J. G., A, Heart at beginning of attack of rheumatic carditis; B, heart size five months later; C, heart size at the end of one year.

to take place was about the same in both groups, namely, 5.8 months as compared with 5.2 months. Change in the size of the heart during rheumatic fever is, therefore, not a sudden, swift process.

The following examples will illustrate the types and variations which were found:

J.G. had three attacks of rheumatic fever within the course of a year. Each attack left her heart notably larger. The third attack produced the greatest degree of enlargement (Fig. 4*A*, *B*, and *C*). It was thought likely that a small pericardial effusion was present, although no friction rub was heard, but most of the increase in size was obviously caused by dilatation and hypertrophy of the myocardium. This case is given emphasis because it shows what tremendous enlargement of the heart may occur in the course of one year.

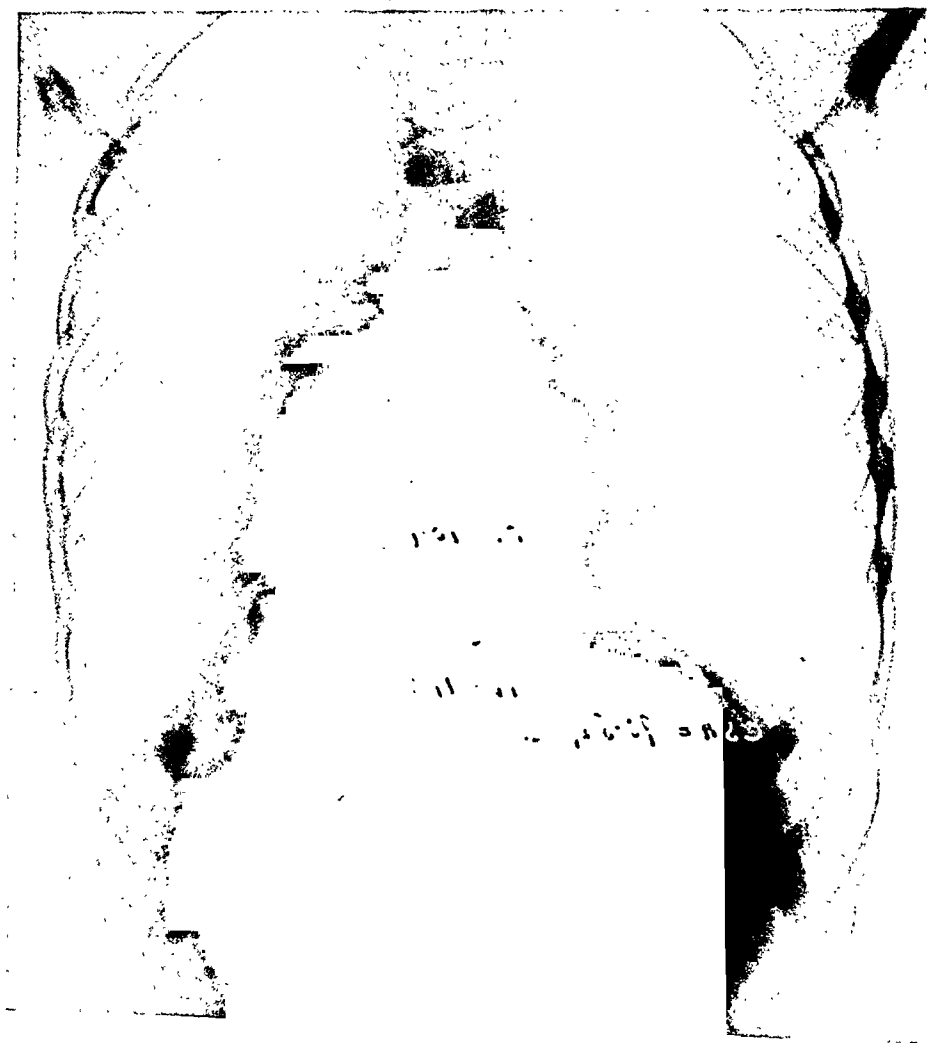


Fig. 4*B*.

R. W. had an attack of rheumatic fever which was moderately severe. The first roentgenogram (Fig. 5*A*) showed enlargement. In the second (Fig. 5*B*) the heart was about the same size, but improvement had occurred in that the left border was much less prominent. This is an important sign of improvement. The child suffered a relapse shortly after the second roentgenogram was taken, and the third (Fig. 5*C*) showed definite enlargement. The patient ultimately died in this attack.

A. D., aged 12 years, had a mild attack of rheumatic fever with slight involvement of the heart. During his illness the heart enlarged, as is shown by the following:

<i>Date</i>	<i>Height</i>	<i>Weight</i>	<i>B.S.A.</i>	<i>T.D.</i>	<i>I.D.</i>	<i>C.S.A.</i>
8/31/38	5'2"	88½ pounds	1.34	10.3	22.3	102.5
12/15/38	5'2"	113½ pounds	1.48	11.8	22.7	106.7

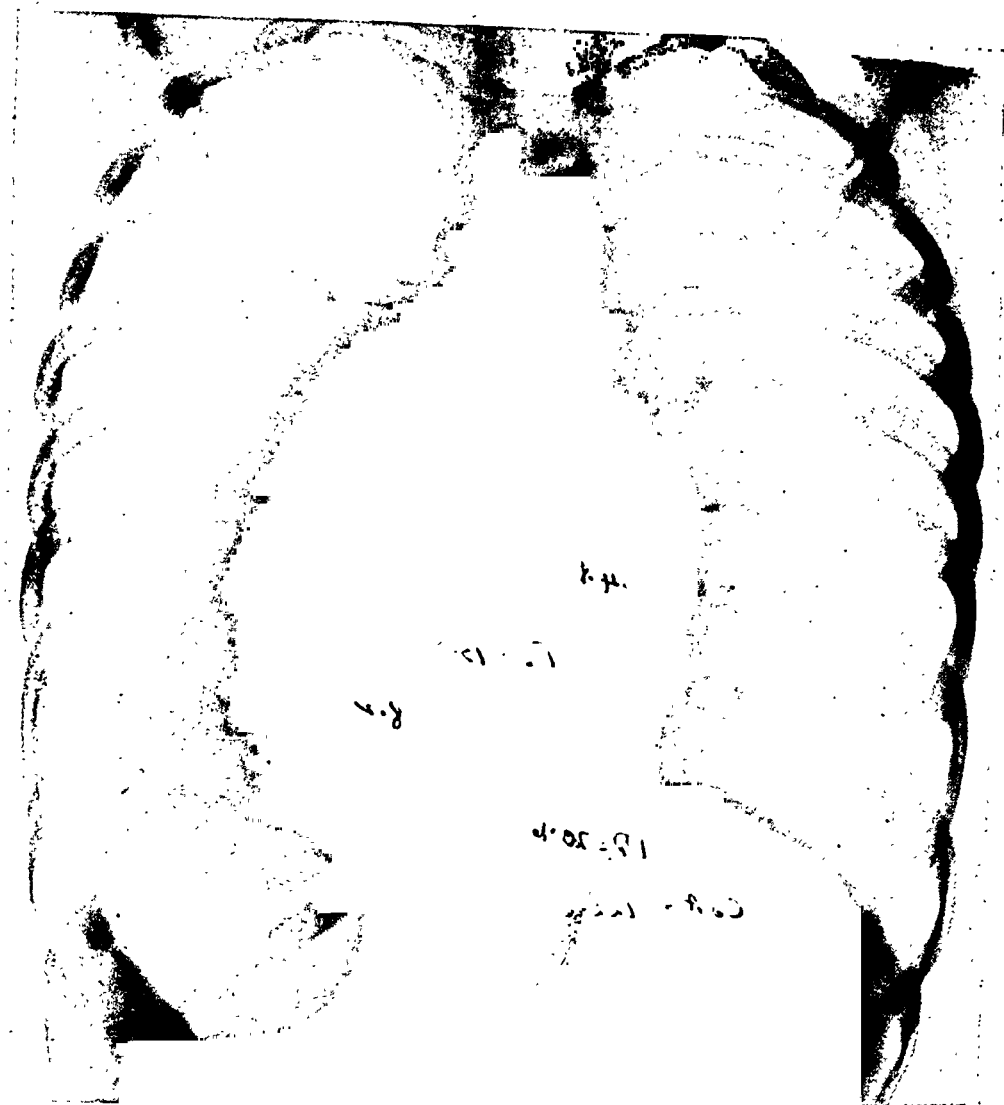


FIG. 4C.

J. W. was admitted to hospital suffering from a moderately severe attack of rheumatic fever and carditis. The sedimentation rate was elevated for two and one-half months. During that time the heart became smaller under treatment, but increased again in size when he was allowed to be up (Fig. 6A, B, and C). This increase in size when the patient gets out of bed is a common occurrence, and shows how sensitive the heart muscle is to any increase in work demanded of it. It must be remembered that a normal heart will become smaller with rest in bed, and will then increase again in size when the patient gets up. Therefore, part of the increase in size with exercise may be normal.

L. S. had chorea, coupled with a moderately severe involvement of the heart. On admission the heart was considerably enlarged, and remained so for the first

month in hospital; thereafter it steadily became smaller. Over the succeeding three months the decrease was very marked, as is indicated in Fig. 7. This is as great a diminution in the size of the heart as we have seen after an acute attack and over the short period of three months. This patient has done exceedingly well, and now, one and one-half years later, no longer has a murmur. The heart measurements are within the limits of normal.

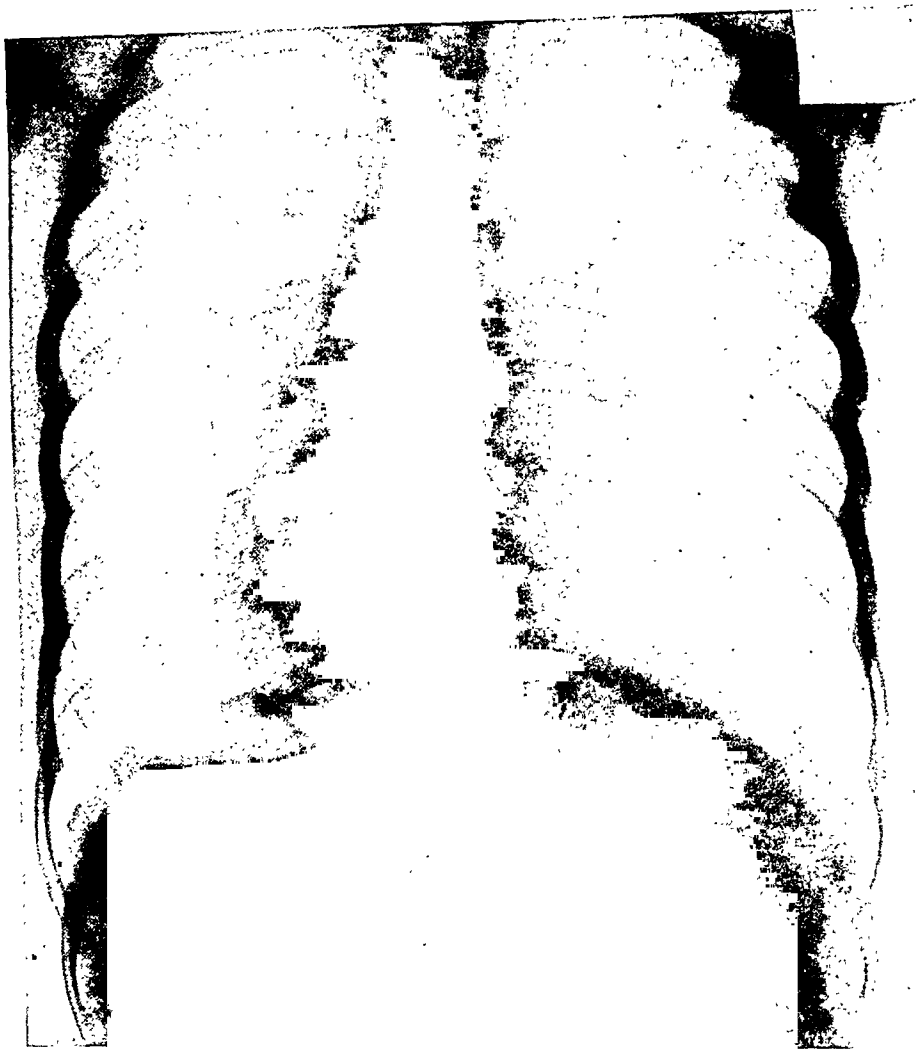


Fig. 5A.

Fig. 5.—J. G., A, Enlargement due to rheumatic carditis; B, heart has decreased in size in three months; C, recurrence of infection produced further enlargement, two months later.

J. B., 12 years old, was admitted with an obvious rheumatic pericarditis. The cardiac shadow was greatly enlarged and showed a rapid decrease in one month (Fig. 8). From our experience, if there is a decrease of 20 sq. cm. in the cardiac surface area in one month, one is almost certainly dealing with pericarditis with effusion. In this case the improvement continued and the heart shadow was within normal limits in three months.

The results shown here indicate a strong ability of the heart muscle to return to a normal condition. With this in mind it is interesting to compare the recuperative power of the myocardium with that of the heart valves. Alterations in the mitral systolic murmur were recorded during the period of roentgenologic study in three groups: (1) murmurs that became louder; (2) those that remained unchanged; and (3) those that became fainter.



Fig. 5B.

The murmur was louder or unchanged in 76 of the 100 cases. This suggests that the restoration of a valve is a much slower process than in the case of muscle. Further evidence of this is the fact that in 60 per cent of the hearts that became smaller there was no change in the murmur or the murmur became louder. Finally, in 8 cases the murmur became louder while the heart was getting smaller. An example of this is the case of R. A. (Fig. 9). He had a moderately severe attack of rheu-

matic heart disease, and over a period of many months his heart became much smaller. At the same time the mitral systolic murmur became harsher and louder. In recent years we have been inclined to over-emphasize the muscle damage. We should remember that, because of the persistence of the valvular scar tissue, when the next attack of rheumatic fever occurs an added strain is placed on the redamaged muscle, and the prognosis is made that much worse. It is the muscle that finally fails, but it is the valve that contributes (sometimes decisively) to the ultimate failure of the muscle.



Fig. 5C.

COMMENT

The study by Taussig and Goldenberg⁴ covered many years, and they divided the patients into three groups, according to the size of the heart: (1) Those whose hearts were not enlarged at the time of the original attack, but became larger over the years, as would be expected with

normal growth. (2) Those whose hearts enlarge with rheumatic infection, and then remain stationary while the chest and the rest of the body catch up; the result is that the size of the heart may ultimately be regarded as normal. (3) Those that show progressive enlargement of the heart beyond the degree anticipated by normal growth.



Fig. 6A.

Fig. 6.—J. W. A, Heart at beginning of attack of rheumatic carditis; B, heart size after five and one-half months in bed; C, heart size after being allowed up gradually. This roentgenogram is 2 months later.

The balancing factor through their study was that of body growth. In the present investigation, which is confined within the limits of a year, the interval is too short to be influenced notably by growth. It appears likely that one of the factors which is responsible for normal heart growth is modified or withdrawn when a child is put to bed and can no longer run and play. In our study, therefore, the stimulus to enlargement was mainly the rheumatic infection.

Taussig and Goldenberg⁴ found that valve damage may occur without cardiac enlargement. Many instances of this have been noted in our study. It follows from this, of course, that one may have active rheu-

matic infection of the heart without any cardiac enlargement. All who had enlargement had accompanying signs of rheumatic activity. Dr. Taussig believes that there is no essential difference between hypertrophy of the heart in response to the abnormal stimulus of disease and the normal stimulus of growth. Her observations emphasize in a refreshing manner the paramount importance of rest to the heart as long as any abnormal stimulus is present. It is our belief that if life could be maintained with 10 to 20 heart beats per minute, the resulting rest would probably eliminate rheumatic muscle and valvular disease as causes of death or crippling.



Fig. 6B.

During the course of our investigation the superiority of the roentgenologic method over clinical examination frequently made itself evident. The limitations of roentgenology are not nearly as great as those of palpation and percussion. A difference in rate or force of beat will often simulate a change in the size of the heart. It may be

difficult to evaluate a roentgenogram of the heart when it is close to normal, but small changes in size can be much more accurately detected radiographically than by physical examination. Furthermore, the roentgenogram constitutes a record that can be kept for further reference, whereas cardiac size, as estimated by clinical methods, is difficult to remember and record.

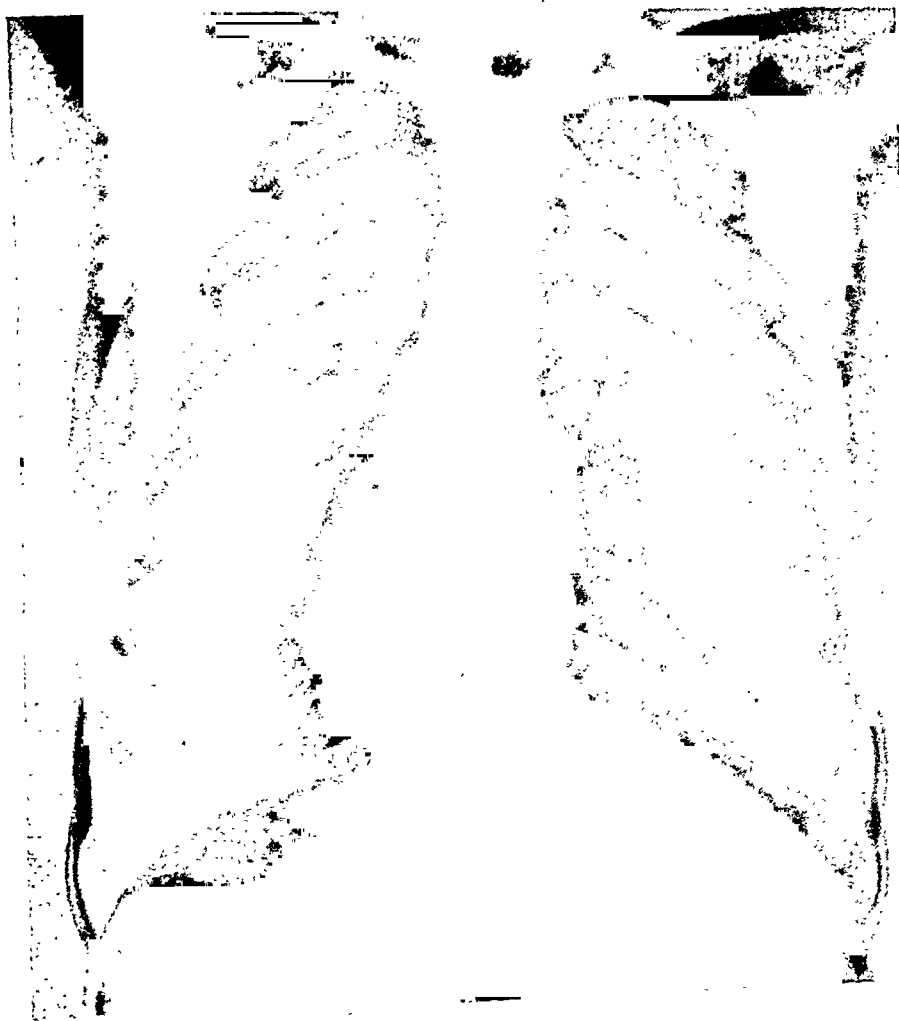


Fig. 6C.

In the past, autopsy has often revealed pericarditis when the diagnosis was not made during life. A friction rub may not be heard in more than about 20 per cent of such cases, so that we look to roentgenologic examination for further diagnostic aid. There are two chief points in the diagnosis: (1) the shape of the heart, and (2) the rapid changes in size. The first is exemplified by an enlarged cardiac shadow which is particularly prominent in the left upper border, and is usually surrounded by evidence of mild atelectasis and congestion of the lungs. We have found the cardiohepatic angle of little value in the diagnosis. The second factor has been studied in this investigation. It has been

found that if the heart shadow decreases rapidly in size in one month (20 sq. cm.), it is almost invariably because of absorption of pericardial fluid. In this way a suspicion can be confirmed. Dilatation of the heart, on the other hand, even with the most rapid recovery, takes longer than this.



Fig. 7A.

Fig. 7.—L. S., *A*, Enlarged heart due to rheumatic carditis; *B* and *C*, marked decrease in size with treatment over a period of three months.

A problem that continually made itself evident during this study was that of the differential diagnosis of carditis and valvulitis. We have depended on the presence of a heart murmur to make a diagnosis of myocarditis, as well as endocarditis, but the murmur may be caused by either or both. An attempt to differentiate these two is a refinement in diagnosis that should be studied further. The following points were set down during the course of the investigation and are presented with the hope of stimulating criticism:

A. Myocarditis. (1) Enlargement of the heart, i.e., an increase in size over a short time, as shown in repeated roentgenograms, or a definite increase over normal. (2) An apical systolic murmur, blowing in quality, which appears during a rheumatic attack is presumptive

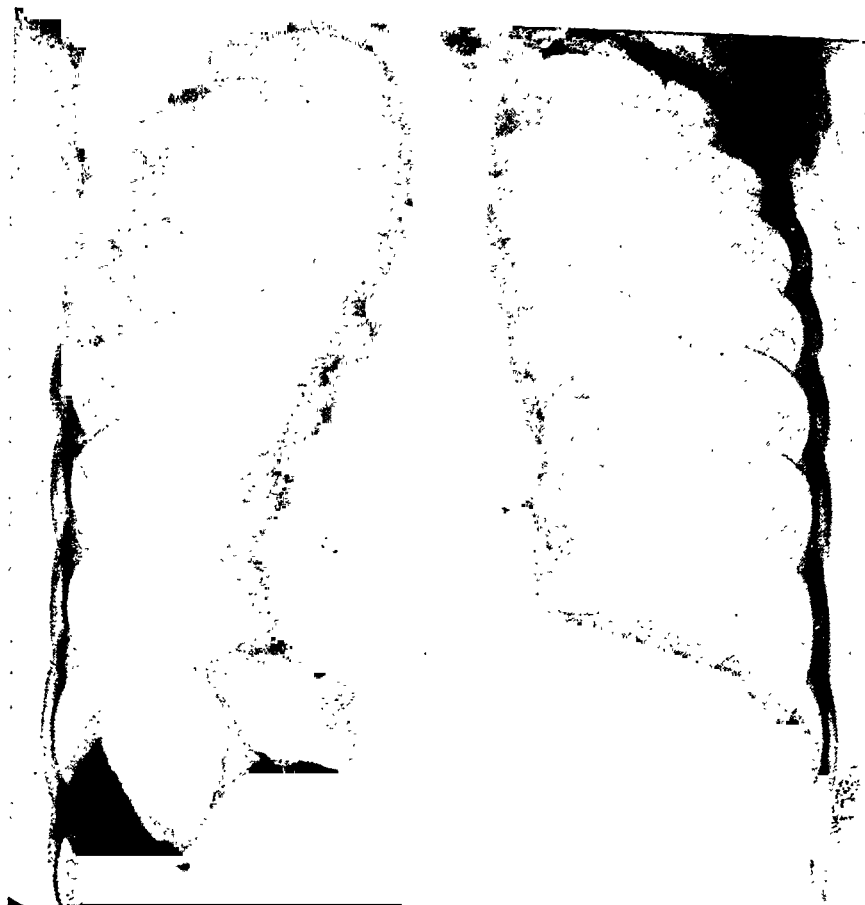


Fig. 7B.

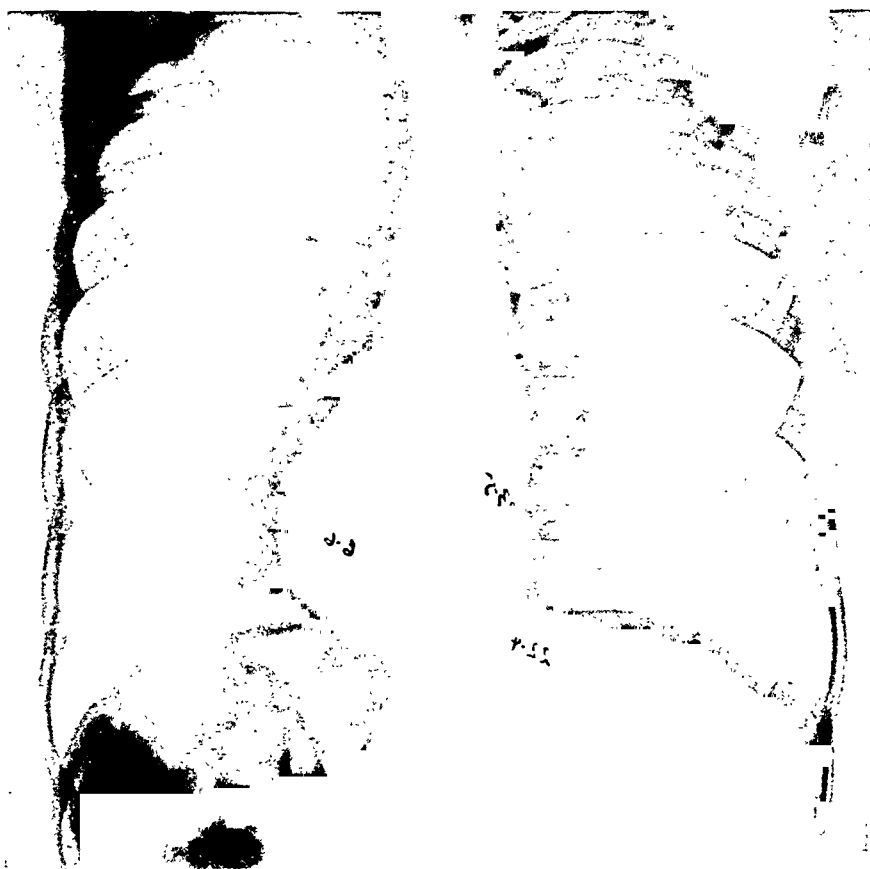


Fig. 7C.

evidence of myocarditis. If the murmur disappears within four months, it is evidence that the myocardium has been affected without involvement of the valve. (3) Increase of the P-R interval of the electrocardiogram above 0.18 second during an attack of rheumatic infection. (4) Accentuation of the third heart sound is probably evidence of myocardial disease.

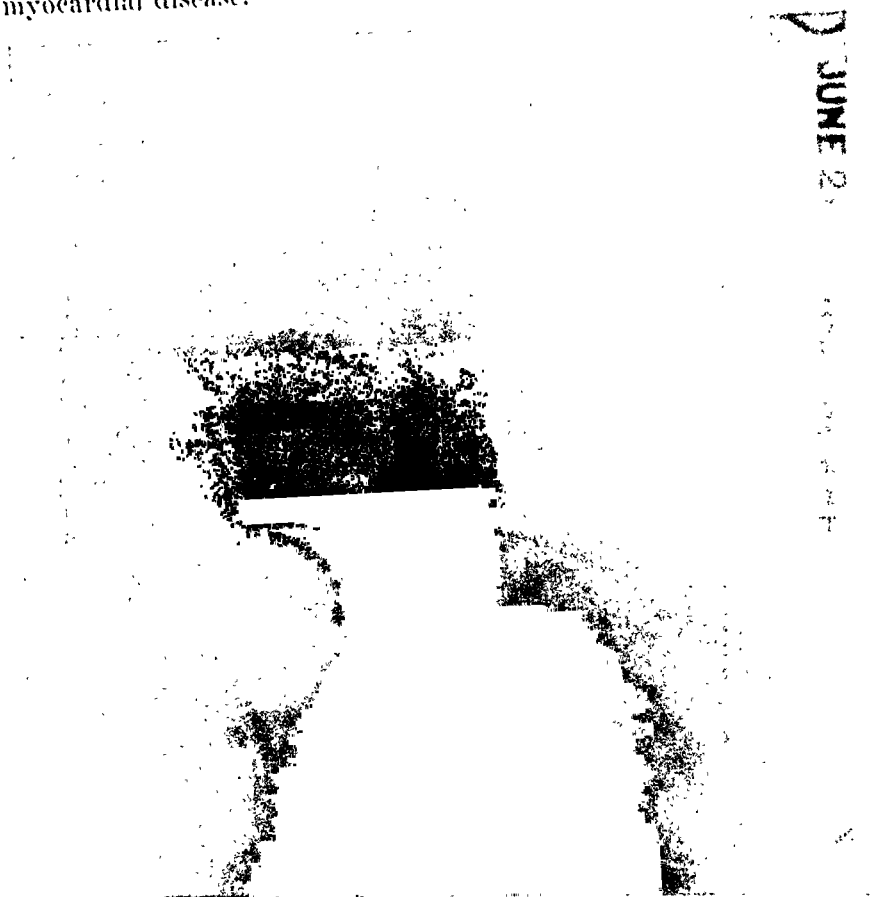


Fig. 8.

Fig. 8.—J. B. A, Enlargement of heart shadow due to rheumatic pericarditis; B, taken three weeks later; C, taken two weeks later again, indicating very rapid absorption of the fluid.

B. Valvular disease. (1) Apical systolic murmur, transmitted to the axilla, which has been present for four months. (2) A mitral diastolic murmur. (3) Aortic diastolic murmur which has been present for four months. (4) A soft, lightly blowing systolic murmur at the apex may be due to dilatation, whereas a harsh apical systolic murmur suggests valvular damage.

Table I indicates the notable ability of the size of the heart to return toward normal. This depended mainly on rest in bed. In general, it was related to subsidence of the rheumatic infection, but enough hearts became smaller while infection persisted to show that this is not con-

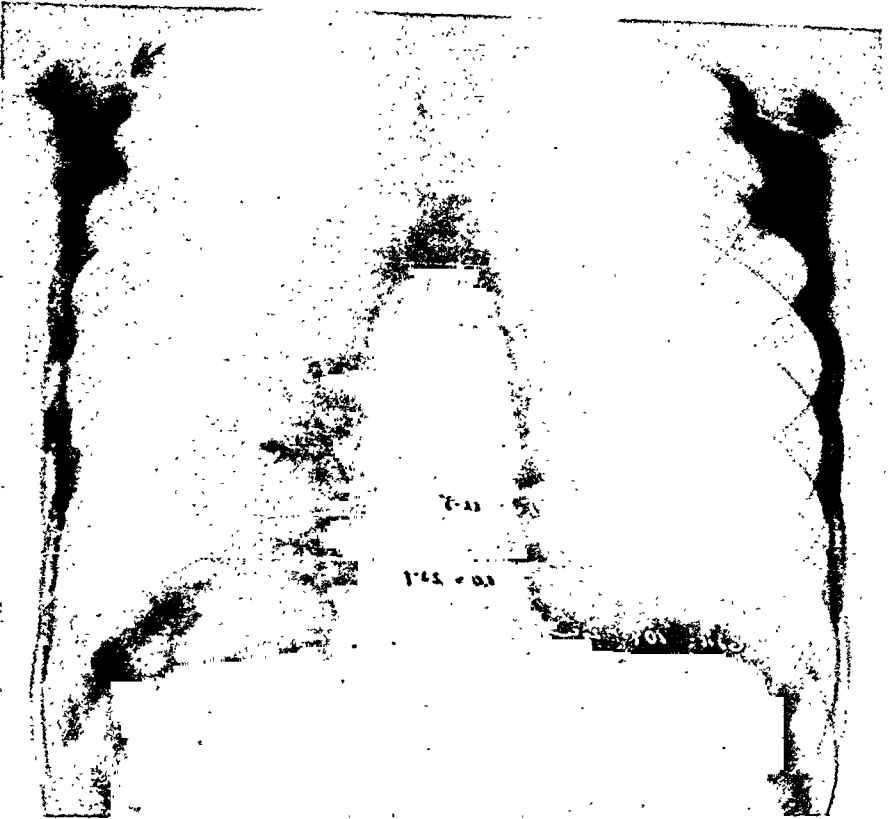


Fig. 8B.



Fig. 8C.

tinually so. Many cases impressed us with the shortness of the time in which a decrease in size took place; it was often in a few months, rather than a year or two. In these patients the enlargement must have been caused by dilatation of the heart.

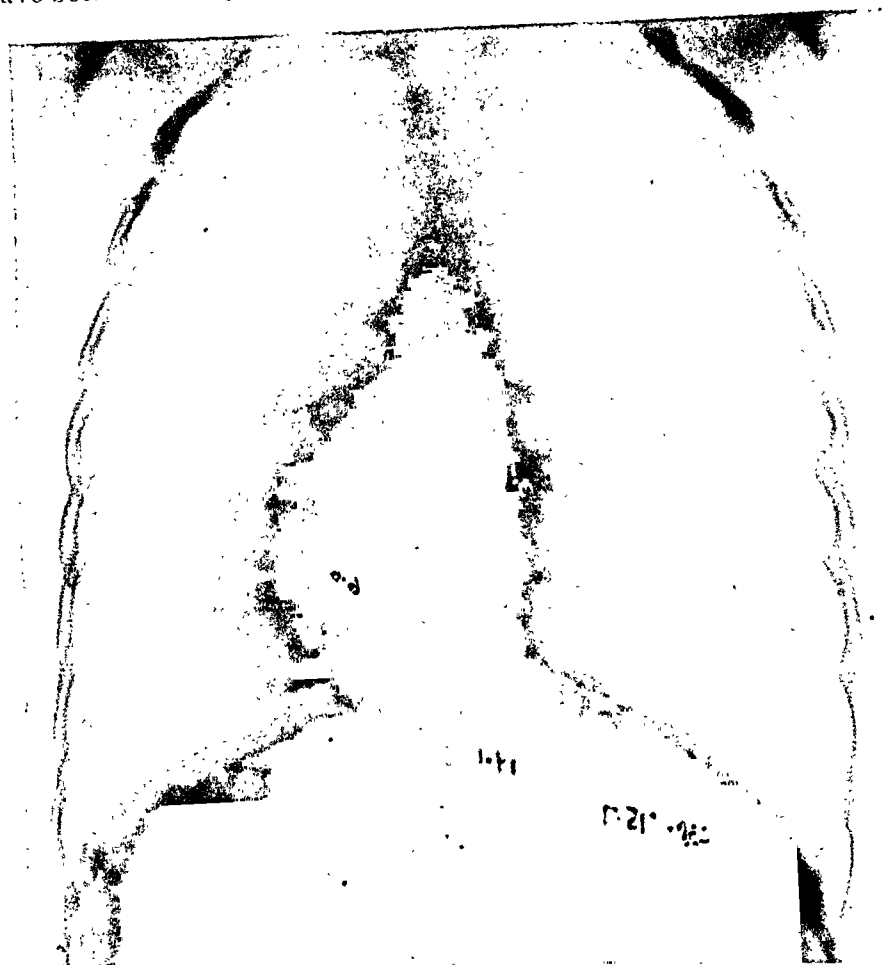


Fig. 2A.

Fig. 2.—R. A., A, B, and C show a steady decrease in heart size in rheumatic carditis. At the same time the mitral systolic murmur became steadily louder and better transmitted.

However, the term dilatation should be used in rheumatic heart disease with caution and a true perspective, because a rapid change in the size of the heart over a few days does not appear to occur except on rare occasions. It is possible that an overwhelming, rapidly fatal rheumatic infection may cause more obvious acute dilatation than was shown in this group, but we could not make roentgenograms in such cases. The patient (J. E.) with paroxysmal tachycardia, with a rate of 240 beats per minute, showed that a marked dilatation can occur in three days. However, such instances are few and far between, and

the general run of hospital cases represented in the 100 instances tabulated here reveals none with such rapid enlargement. Table I indicates that regardless of whether the heart enlarges or becomes smaller, it usually takes three to five months for considerable alteration to become apparent. When the heart is at rest and the infection is subsiding, the maximum decrease may be expected. When active infection continues and the patient is not put to bed, the maximum enlargement of the heart may be looked for.

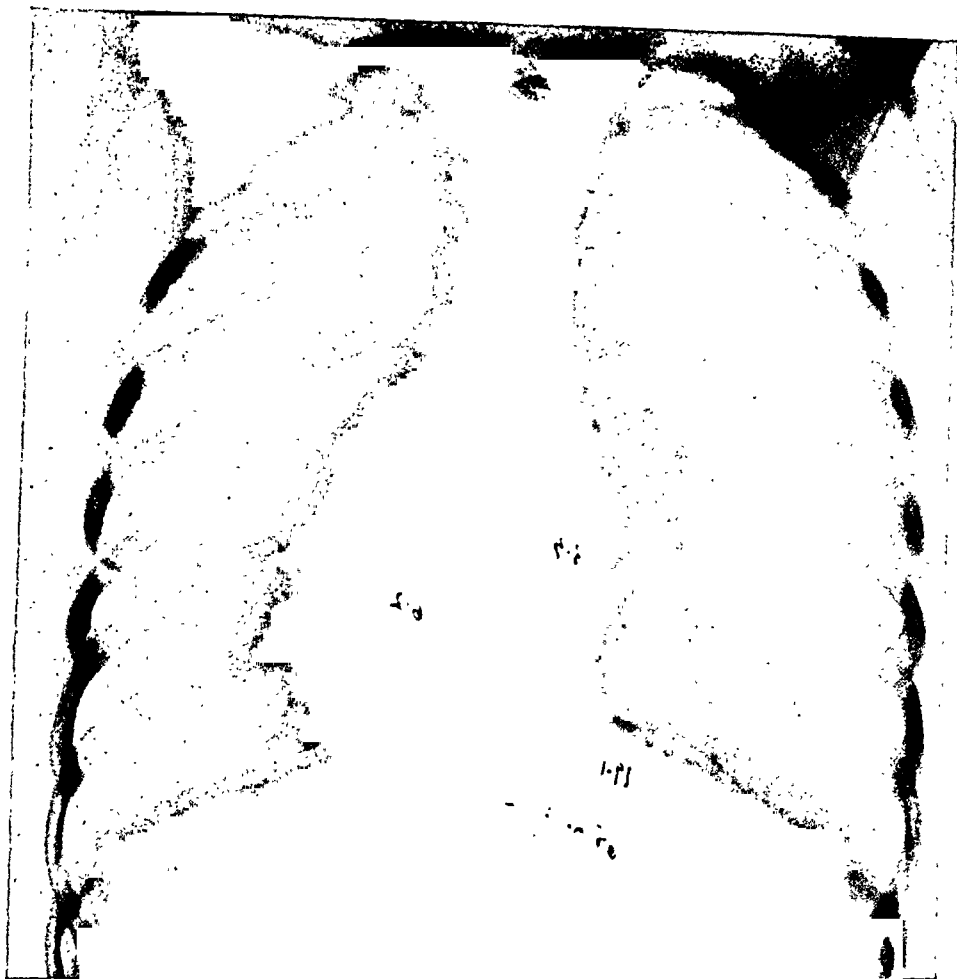


Fig. 9B.

SUMMARY

1. It is very difficult to ascertain degrees of change in the size of the heart by physical examination alone. Roentgenologic examination gives more accurate data.
2. Acute dilatation, with a dramatic change in the size of the heart, does not seem to occur (except under rare circumstances).
3. A moderate, initial increase in the size of the heart can take place within two or three weeks, but enlargement appears to occur slowly at any stage of the disease.

4. A fairly marked increase in the size of the heart may occur in five or six months, but the average change in this time is not great.
5. A notable decrease in size may occur in five months, but the usual change in this interval is not great.
6. When change in size in one month is more than 20 sq. cm. in the cardiac surface area, pericarditis is probably present.

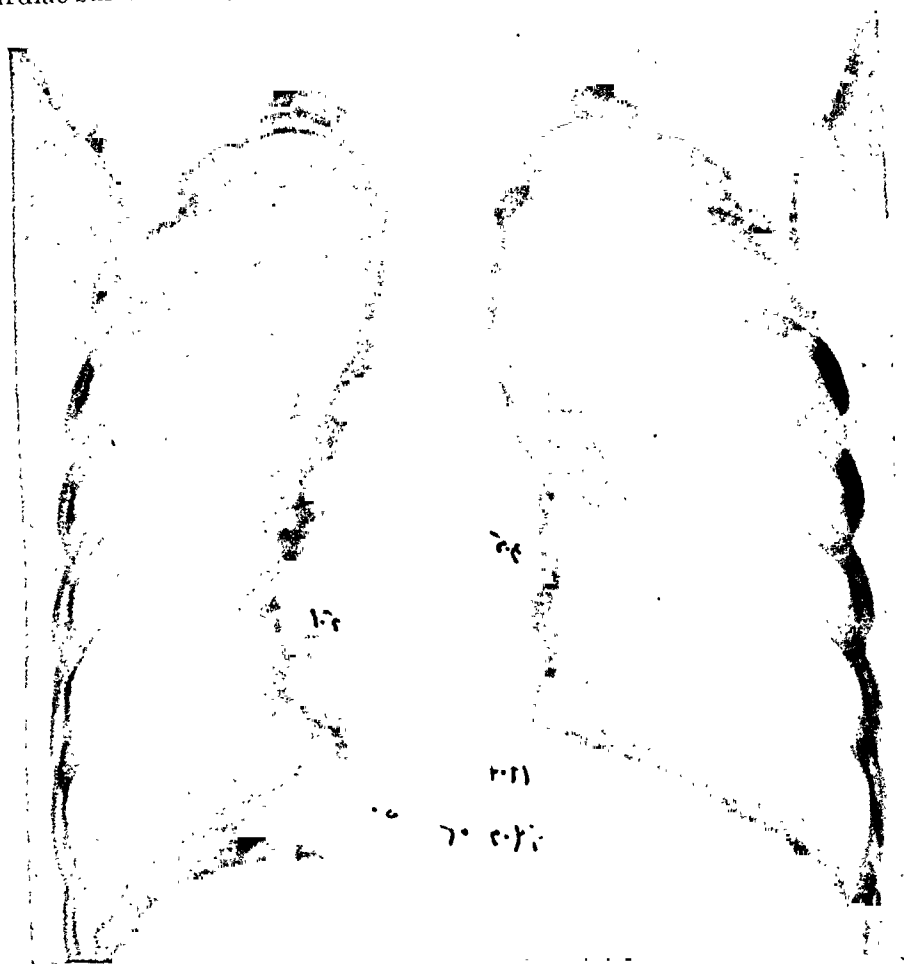


FIG. 9C.

7. The prognosis is obviously better, on the whole, if heart is getting smaller, rather than larger.

8. The heart muscle shows greater recuperative powers than the heart valves. Improvement is more striking in the muscle than in the valve.

9. Roentgenologic examination aids in differentiating between myocardial and valvular disease.

10. In most cases the progress of a patient can be estimated better by studying the size of his heart than by studying the murmur.

11. Bradycardia is more likely to produce cardiac enlargement than tachycardia (certain cases of paroxysmal tachycardia excepted).

12. Continued rest in bed reduces the size of the heart when no disease is present.

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LUTEMBACHER'S SYNDROME AND A NEW CONCEPT OF THE DYNAMICS OF INTERATRIAL SEPTAL DEFECT

M. H. UHLEY, M.D.^{*}
MILWAUKEE, WIS.

LUTEMBACHER'S SYNDROME

THE coexistence of an interatrial septal defect and mitral stenosis is not frequently encountered. Martineau,¹ in 1865, reported the first case. In 1916, one year after Maude Abbott reported a case,² Lutembacher³ summarized the reports available up to that time, offered a concept of the probable genesis of these lesions, and discussed the effect upon cardiodynamics. The presence of both interauricular septal defect and mitral stenosis has consequently been designated as Lutembacher's syndrome. The paucity of case reports in the earlier medical literature can be appreciated by the fact that when McGinn and White⁴ reviewed the subject in 1933, and added a case of their own, the total number of cases was twenty-four. Since then, isolated reports by Jerofejeff,⁵ Mitchell and Bauer,⁶ Kirschbaum and Perlman,⁷ and a review of eleven additional cases by Tinney⁸ have appeared.

The initial series of twenty-four cases contained only two males, Söldner's,⁹ and McGinn and White's.⁴ This disparity in incidence between the sexes, however, is less evident in subsequent reports. At present, with this case, there are in all twelve males and twenty-seven females.

This syndrome is not incompatible with prolonged life. Firket,¹⁰ in 1880, described the case of a 74-year-old woman who had survived eleven pregnancies. Lutembacher³ reported another case in a woman, aged 61 years, who had had seven pregnancies. Sailer's patient¹¹ lived to be 67 years, and our case is that of a man who is 60 years of age. Generally speaking, however, the life expectancy is considerably less. Eleven of the twenty-four patients in the McGinn and White series died on or before reaching the age of 30; the average age at the time of death was 35.

ORIGIN OF THE SEPTAL DEFECT AND THE MITRAL STENOSIS

The lesion in the interauricular septum is readily explained embryologically. Thin, sickle-shaped membranes, arising from the endocardial cushions, one on the dorsal, the other on the ventral, portion of the

^{*}Recent Fellow in Medicine, University of Minnesota, and Resident in Medicine, Minneapolis General Hospital, Minneapolis.
Received for publication Jan. 19, 1942.

atrial part of the original single atrioventricular canal, grow downward and unite in the *midline*, forming right and left atrioventricular canals. From the atrial roof the septum primum grows downward to attach to this newly formed ridge between the canals. Meanwhile the septum primum becomes thinned and perforates in a previously intact region, thereby forming foramen ovale I. In the seventh week of fetal life, a second septum makes its appearance just to the right of the septum primum. It is *incomplete*, and its foramen is known as foramen ovale II. The growth of these two partial atrial septa is such that the main expanse of the septum primum overlaps foramen ovale II. It serves as a flap which permits blood to pass from right to left, but not in the reverse direction. This condition obtains until after birth, when there is a decrease in pressure in the right auricle and/or an increase in pressure in the left auricle, and the two membranes become closely apposed and gradually fuse into a single atrial septum.¹²

Failure of the septum primum to descend or to attach properly, or a persistent defect in the septum primum or secundum lays the groundwork for Lutembacher's syndrome.

The question of the origin of the mitral lesion, i.e., whether it is congenital or acquired, was at one time much mooted, but now there is almost general agreement that it is acquired. Early, Lutembacher,³ postulating a congenitally stenosed mitral valve, felt that the elevation of pressure in the left auricle caused by the stenosed valve prevented proper closure of the foramen ovale, and hence caused a reversal of the usual flow through the fetal heart. Firket¹⁰ was of the opinion that the combination of congenital mitral valve deformity and abnormality of the interauricular septum was a fortuitous coincidence which served to safeguard against the pulmonary congestion that would result from the mitral lesion alone. Dressler and Roesler¹³ are proponents of the theory that an increase in left auricular pressure, such as probably occurs after birth, would favor closure of the foramen ovale because of the oblique course of the canal. Furthermore, they hold that a small, congenital, interauricular septal defect, complicated by an acquired mitral stenosis, would in time become much enlarged because of dilatation resulting from the increase in pressure within the left auricle. McGinn and White are in agreement with these authors.

A definite history of rheumatic fever was obtained in three of the twenty-four cases reviewed by McGinn and White. The absence of a rheumatic fever history does not militate against the likelihood of acquired endocarditis in these cases, for many patients with proved rheumatic endocarditis never give histories of having been ill with rheumatic fever. In the clinical experience of Dr. George Fahr, Chief of Medicine at the Minneapolis General Hospital, about 25 per cent of the cases lie in this category. Pathologists report figures up to 50 per cent for this group.

The interesting observation of Maude Abbott¹⁴ that atrial septal defects are frequently associated with abnormalities in the structure of the mitral valve leaflets suggests the possibility that disturbed stress-strain phenomena may more readily predispose these leaflets to rheumatic endocarditic changes. Almost three-fourths of Roesler's¹⁵ 62 patients with interatrial septal defect also had chronic valvular lesions.

DIAGNOSIS

Clinically, the diagnosis is a difficult one. The auscultatory signs are quite variable, depending upon the degree of involvement of the mitral valve, i.e., degree of stenosis and insufficiency, degree of enlargement of the heart, and the presence or absence of failure. The size of the interauricular defect is a factor which may account for other auscultatory signs at the base of the heart. The electrocardiogram offers only suggestive evidence if right ventricular preponderance and abnormal P waves are present. The clinical data, when correlated with roentgenographic study, however, may point strongly to the diagnosis.

Assmann,¹⁶ and with slight modification, Dressler and Roesler,¹³ suggest a diagnostic roentgenologic tetrad consisting of: (1) Extensive right-sided dilatation and hypertrophy; (2) very wide hilar lung shadows; (3) large conus; (4) narrow or hypoplastic aorta.

In two instances the pronounced hilar shadows produced by the marked dilatation of the pulmonary arterial tree led to a mistaken diagnosis of mediastinal tumor. After a poor response to irradiation, one of these patients was operated on, and the mass was found to be an aneurysmal dilatation of the pulmonary artery in which there was a clot.²⁴

CASE REPORT

The case is that of a white man who was 60 years of age at the time of his final admission to the Minneapolis General Hospital, Feb. 11, 1941. Only relevant data from the records of hospital admissions and from the post-mortem observations are presented.

When seen for the first time, June 21, 1938, in the Out-Patient Department, the patient complained of occasional dyspnea, choking sensations, and associated palpitation. He gave a history of diabetes mellitus for seventeen years. A systolic murmur was heard at the apex. The heart was found to be slightly enlarged to the left on percussion. The blood pressure was 122/80. The blood, serologic reactions, and urine were normal.

The patient was admitted to the hospital March 7, 1939, complaining of occasional dyspnea on exertion, and of generalized joint stiffness and painful joint motion. These latter symptoms had been present for several years but recently had become progressively worse. A history of what might have been rheumatic fever at the age of 16 was obtained. The heart was enlarged to the left, and a loud systolic murmur was heard over the entire precordium, but loudest at the apex. The blood pressure was 156/78. A roentgenogram of the chest showed enlargement of the heart of the right ventricular type; the transverse diameter measured 15 cm. There were a distinct prominence of the pulmonary conus and

questionable pressure on the barium-filled esophagus. The electrocardiogram showed left ventricular preponderance, with slightly depressed S-T, and slightly elevated S-T₂. The P-R interval was 0.22 second. The blood and urine were normal. The patient was discharged after his diabetes had been brought under control and his joint symptoms were relieved.

On Feb. 7, 1940, the patient returned with a severe upper respiratory infection. Basilar râles were heard posteriorly on the left. A loud systolic murmur was heard over the entire precordium, especially at the third and fourth intercostal spaces along the left sternal border. The pulmonic second sound was accentuated. No thrills were felt. The liver was palpable two fingerbreadths below the right costal margin. The blood pressure was 168/78. Roentgenologic examination failed to reveal any evidence of pneumonia; the right-sided enlargement of the heart was again noted.

The patient was admitted to the hospital Sept. 20, 1940, complaining of shortness of breath and choking sensations for three months, and swelling of the ankles for one month. Dyspnea and orthopnea were evident on examination. Bilateral basilar râles were heard. The heart was enlarged to the left on percussion, and a diffuse apical beat was noted. A soft systolic murmur was heard at the apex. The liver was palpable two to three fingerbreadths below the right costal margin, and edema of the ankles was present. The blood pressure was 188/96, and the venous pressure was 26 cm. of citrate solution. Congestion of both lung fields and a small pleural effusion on the left were demonstrated roentgenologically. The heart was enlarged, and the transverse diameter measured 15.6 cm. The electrocardiogram showed, from time to time, nodal rhythm and complete heart block. Partial A-V block, with the Wenckebach phenomenon, was seen in one record. The patient responded to digitalis, and the diabetes was brought under control before discharge.

The patient was admitted to the medical service Feb. 11, 1941, complaining of shortness of breath and swelling of the face, abdomen, and ankles for one month. Cyanosis of the lips, mucous membranes, and nail beds and generalized edema were noted. The neck veins were prominent. Congestive râles were heard throughout both lungs. The heart was enlarged to the left and right by percussion. A systolic thrill was palpable over the apex, and a presystolic murmur, rough in character, followed by a high-pitched, blowing systolic murmur, was heard at the apex. Occasional extrasystoles were noted. The blood pressure was 160/90, and the venous pressure was 30 cm. of citrate solution. A diagnosis of mitral stenosis and insufficiency was made. Roentgenologic examination revealed enlargement of the heart, with definite pressure on the barium-filled esophagus. Bilateral pulmonary congestion was present. The patient responded poorly to treatment, and died three days after the onset of a pneumonic process. Death occurred on April 20, 1941.

Post-Mortem Examination.*—Evidence of congestive failure was found in the serous cavities, viscera, and peripherally. There was a pneumonic process in the left lower lobe.

Heart.—The heart weighed 440 Gm. There was a small, adherent thrombus in the left auricular appendage. A large defect, low in the interauricular septum, with a diameter of 4 cm., was found. It occupied approximately two-thirds of the interatrial wall. It was oval in shape, and its lower border reached the level of the tricuspid and mitral rings. This defect was not the foramen ovale, for the obliterated foramen could readily be identified somewhat anterior to this defect (Fig. 1).

*The post-mortem report and photographs of the heart were made available through the kindness of Dr. F. C. Andrus, Chief of the Department of Pathology, Minneapolis General Hospital.

The left atrium and ventricle showed little, if any, hypertrophy or dilatation. The right atrium was markedly dilated, and its wall was definitely hypertrophied. The aortic, tricuspid, and pulmonary valves appeared normal grossly. The mitral valve seemed to be composed of three leaflets. There were fewer than the usual number of chordae tendineae, and two appeared to be thickened. The remainder showed no definite thickening or shortening. The valve leaflets were definitely thickened and had rolled edges. The valve was stenotic, and, before the ring was cut, admitted the tip of the small finger with difficulty. The cut surface of the myocardium was relatively normal. Grossly, no fibrosis was seen. There was minimal arteriosclerosis of the right coronary artery. A small hemorrhagic area in the wall of this vessel did not appear to obliterate the lumen to any appreciable extent. The root of the aorta showed a moderate degree of atheromatous degeneration.

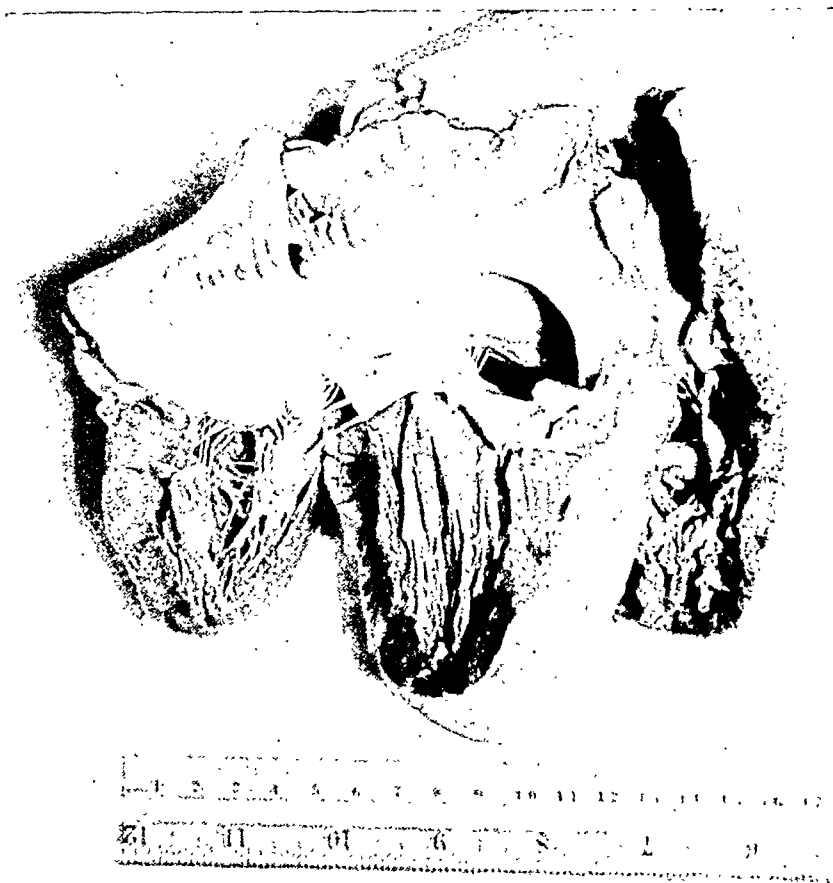


Fig. 1.—The left auricle and left ventricle are exposed to show the thickened, rolled leaflets of the mitral valve, and the split in one of the cusps. The interauricular communication is clearly seen. The thickening and dilatation of the right side of the heart are apparent.

Microscopically, the sections of the heart revealed interstitial edema, as well as slight infiltration with mononuclear cells. There were cellular infiltration and fibrosis about the blood vessels which possibly represented remnants of Aschoff nodules. The mitral valve leaflets showed dense scar tissue, proliferation of fibroblasts, and areas of hyaline necrosis.

Post-Mortem Diagnosis.—Patent interauricular septum primum and mitral stenosis and insufficiency (Lutembacher's syndrome). Pulmonary and generalized edema of congestive failure. Left lower lobe pneumonia.

DYNAMICS OF INTERATRIAL SEPTAL DEFECT

The following discussion is offered in order to correlate the available fundamental data which are necessary for the establishment of a new concept of the dynamic disturbances in Lutembacher's syndrome. However, the concept to be presented applies to all functionally significant interauricular communications, whether or not there is an associated mitral lesion. Since the initial inquiries into the problem were stimulated by a consideration of Lutembacher's syndrome, the discussion will deal first with that entity.

CURRENT CONCEPT

In agreement with Dressler and Roesler,¹³ McGinn and White,⁴ in the most recent view of the dynamics in Lutembacher's syndrome, explain the post-mortem findings as follows:

"The pressure in the left auricle rises because of the stenosis of the mitral valve, and much of the blood passes through the interauricular septal defect rather than through the stenotic valve. The blood that passes from the right auricle to the right ventricle is then passed through the lungs a second time. The right ventricle and the pulmonary arteries dilate while the aorta remains small because of the reduced volume of blood in the systemic side. The interauricular defect increases in size because of the increased pressure in the left auricle due to the mitral stenosis. The strain is primarily on the right heart, and results in dilatation and hypertrophy. The failure of the left auricle to dilate and hypertrophy subsequent to the stenosis is due to the reduction and equalization of pressure with the left auricle by the septal defect."

OBJECTIONS TO THE CURRENT CONCEPT

The foregoing point of view, however, is a consideration of those changes in cardiodynamics which are incident to the development of mitral stenosis. The phenomena noted are "dated" from the onset of that added pathologic state. Yet important, if not the most significant, structural changes have already occurred in a heart in which an interatrial septal defect is present. For it is more than coincidence that the autopsy findings in cases of interatrial septal defect, either with or without an associated mitral stenosis, are strikingly similar. Generally speaking, in both the complicated and uncomplicated forms, the right auricle and ventricle are markedly dilated and hypertrophied, whereas the left side of the heart undergoes little, if any, change. The branches of the pulmonary arterial tree are considerably dilated, but the aorta tends to become hypoplastic. Hence any consideration of Lutembacher's syndrome must, of necessity, take full account of those antecedent dynamic changes which are caused by the interatrial septal defect alone.

Straub¹⁷ has established the fact that left auricular pressure is greater than right auricular pressure in the normal experimental animal. Roesler,¹⁵ in an excellent, comprehensive analysis of sixty-two cases of interatrial septal defect, contends that this same pressure difference causes a flow of blood from left to right in the presence of a septal defect. Absence of cyanosis in these cases (except terminally) is accepted as *prima facie* evidence of the direction of flow by Abbott¹⁴ and Roesler.¹⁵ There is little doubt that flow from left to right auricles does occur, but the evidence that this directional flow is caused by a difference in intra-auricular pressures may be questioned.

The flow of blood through the heart is governed by the same principles of hydrokinetics that apply to flow through any hydraulic system. It would be well, therefore, to review the component factors of flow in such a system.

According to the Bernoulli theorem, neglecting friction, the total head, or total amount of energy per unit of weight, is the same at every point in the path of flow in a hydraulic system.* The total head consists of three factors:

- (1) The kinetic energy factor, $\frac{v^2}{2g}$
- (2) The potential energy factor, h , due to the height above a given datum plane, and
- (3) The potential energy factor, $\frac{p}{w}$, or, head of pressure.

The theorem simply states that the sum of these three factors at one point in the stream must be equal to the sum of these factors at any other distal point.

However, since fluids in motion invariably suffer a loss of energy through friction, this loss is accounted for by adding the factor " f ," to the right-hand side of the Bernoulli equation. Thus,

$$\frac{v^2}{2g}L + \frac{p}{w}L + h_L = \frac{v^2}{2g}R + \frac{p}{w}R + h_R + f$$

It must be inferred from Roesler's explanation that the energy head in the left auricle is greater than that in the right by virtue of the pressure difference. If this were the important factor, one would expect to find enlargement of the left auricle, perhaps exceeding that of the right. For it is generally accepted that the differences in work demanded of the various chambers of the heart determine physiologic or pathologic dilatation and hypertrophy, or both, of the respective chambers. When there is an increase in pressure within a chamber, that chamber is called upon to do more work than one with a lower pressure.

*It should be noted that the Bernoulli theorem, as stated, applies to any stream in which all particles in any cross section have uniform flow. However, the three factors of the Bernoulli equation which follow are applicable as well to streams of varying cross section and nonuniform velocities, by slight modification of the formula.

This is well borne out by the phenomena which are known to occur during the normal growth of the heart. At birth the walls of the right and left ventricles are approximately equal in thickness; the right is slightly thicker in the ratio of 8:7.¹⁸ In time, the left ventricular musculature increases in thickness. This is the result of the rapid expansion of the systemic vascular bed, which parallels body growth and increases peripheral resistance, and this demands an increased head of pressure in the left ventricle. In contrast to this, the relatively slowly changing resistance in the pulmonary bed makes a much smaller demand on the right ventricle. Because of the disparity in heads of pressure necessary for flow in the distinctly separate circuits, the left ventricular wall becomes measurably thicker than the right within three to four months after birth, according to both Gross¹⁹ and Müller.²⁰ By the end of the first year of life, this ratio is approximately 2:1.²¹

A change in the auricular musculature must also occur after birth, although to a much less extent than in the ventricles. Auricular systole, which contributes about 5 to 10 per cent to the respective total ventricular blood volumes, occurs at a time when the ventricles are completely filled. Therefore, the final auricular contribution must be expelled with sufficient force to distend further the filled ventricles, and the left auricle must exert a greater ejection force than the right auricle in order to transmit its distending pressure to the heavier muscled left ventricle. Thus there is established the adult ratio of left to right auricular thickness of 3:2 or 2:1.

A comparable "demand-response mechanism" must obtain in the pathologic as well as the physiologic state. Accordingly, if, as Roesler states, the left auricular pressure is greater than the right, and causes a flow from left to right, the left auricle should show a degree of enlargement at least equal to, if not greater than, that of the right. Yet necropsy specimens in cases of interatrial septal defect, whether simple or complicated by mitral stenosis, show marked structural changes in the right auricle, and the left auricle is almost completely spared. Hence, some mechanism other than a pressure difference must account for the ultimate cardiac changes.

NEW CONCEPT OF THE DYNAMICS OF INTERATRIAL SEPTAL DEFECT

A consideration of the various factors in the Bernoulli theorem affords an opportunity to view such possibilities critically. Of these factors, one which has previously been given no consideration to my knowledge is the potential energy factor, "due to the height above a given datum plane."

If one visualizes the projection of a heart in three-dimensional space, noting axial and planar relationships, this new possibility presents itself. For, if the auricular axial plane is such that the left auricle is

placed above the right, and the patent septum lies in the floor of this upper chamber, it is conceivable that a gravitational factor would determine the direction of flow of blood between the chambers. This gravitational shunting of blood would throw a considerable load upon the right side of the heart, and perhaps set up the dynamic state which leads to the characteristic changes in hearts with a septal defect.

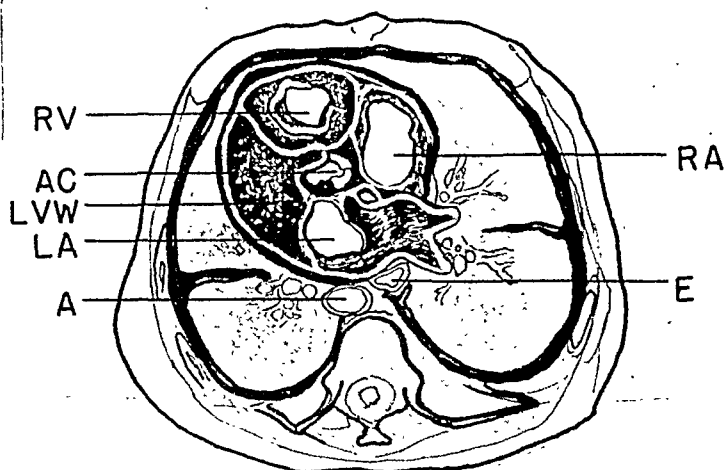


Fig. 2.—Horizontal section viewed from above, at the level of the upper border of the fourth rib (body of newborn infant). RV, Right ventricle; AC, aortic cusps; LVW, left ventricular wall; LA, left auricle; A, aorta; RA, right auricle; E, esophagus. This drawing was made from a photograph in the original article, as quoted, and is reproduced with the permission of Dr. J. C. Gittings.

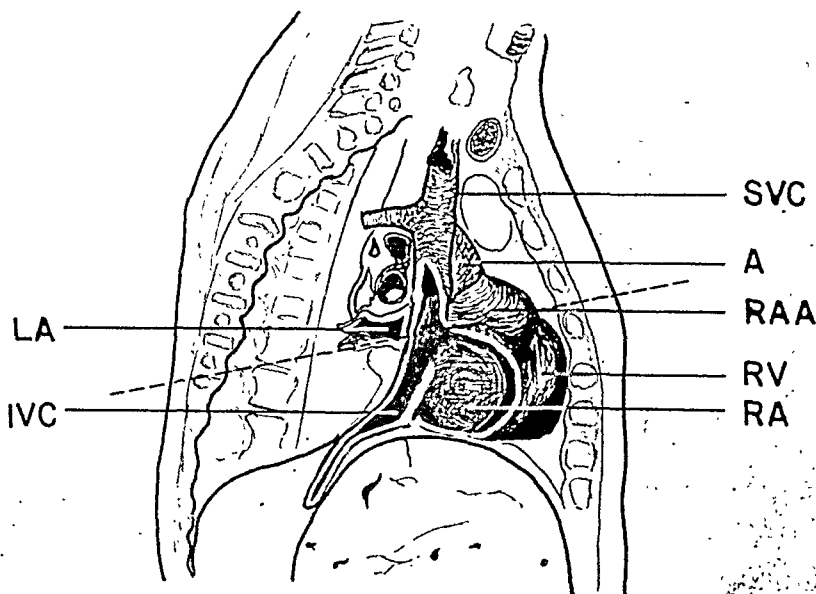


Fig. 3.—Sagittal section, viewed from the right; the plane of the section is 0.75 cm. to the right of the midsternal line (body of newborn infant). LA, Left auricle; IVC, inferior vena cava; SVC, superior vena cava; A, aorta; RAA, right auricular appendage; RV, right ventricle; RA, right auricle. The broken line represents the approximate plane of the foramen ovale. Copied from a photograph with the permission of Dr. J. C. Gittings.

About thirty years ago, a classic study on the anatomic relationships of intrathoracic structures in newborn infants was made by Fetterolf and Gittings.²² The authors injected the bodies with a 10 per cent formaldehyde solution and froze them. Numerous dissections and horizontal and sagittal sections were made through various portions of the thorax. Two drawings from their photographs are here reproduced (Figs. 2 and 3). The first, a horizontal section through the thorax, shows the relationship of the auricles in that plane. The second, a sagittal section, shows the left auricle in a definitely more cephalad position than the right auricle, and, what is most significant, the plane of the foramen ovale. Quoting the authors, "The foramen ovale lies in an almost horizontal plane, and not vertically, as is commonly supposed." Here, then, is anatomic evidence in support of the proposed concept.

AN EXPERIMENTAL PROCEDURE

Simple laboratory methods afford an opportunity to note the flow changes in a two-chamber system with a common patency. Two condoms are rubber-cemented together, while uninflated, and, after cohesion occurs, a communication is established in their common wall. A U tube, with inflow source, is fitted into the proximal free ends, and tubes of smaller diameter are tied into the distal ends (Fig. 4). The two chambers are placed in the same horizontal plane, and the septum, therefore, occupies a vertical plane. The system is filled with water, and, when the inflow rate is sufficient to maintain a slight but unvarying distention of the chambers, that rate is kept constant. It is noted that the trajectories of fluid from the two outflow orifices is identical in pattern and distance. Also, if the escaping fluid is collected in separate containers, it is seen that in a given period of time the volume flows are identical.

The assembly is now turned so that one chamber lies above the other, i.e., the communication is in a horizontal plane (Fig. 4 should now be labeled "seen from the side"). Even though the rate of inflow to the system is kept constant, as before, the lower chamber is seen to dilate slowly, whereas the size of the upper one decreases somewhat. When equilibrium is again established, the pressure in the lower chamber is greater than that in the upper chamber for (1) it is larger; (2) the trajectory from the lower chamber extends beyond that of the upper chamber; (3) the rate of outflow from the lower chamber is greater than that from the upper chamber.* These differences are attributable to the difference in height between the respective streams above a given horizontal datum plane.

*Sample readings at 25 seconds:

Upper chamber outflow, 192 c.c.

Lower chamber outflow, 205 c.c.

Thus we see that if two chambers with a common communication are so disposed that the septum containing the communication lies in a vertical plane, if the inflow rate is constant and the outflow orifices are of the same diameter, there need be no mixing of the contained fluids; in fact, the assembly functions as if there were no communication between the chambers. But when the two chambers are placed in a position so that the communication lies in a horizontal plane, i.e., so that one chamber lies above the other, it is seen that the lowermost chamber dilates, that there is a definite increase in pressure in that chamber, and that an increase in the rate of outflow occurs, with corresponding opposite changes in the upper chamber.

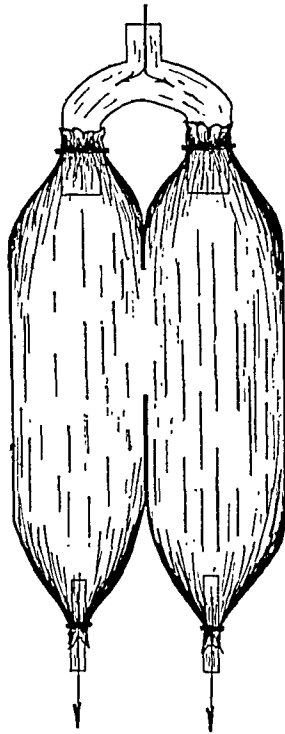


Fig. 4.—Experimental assembly, viewed from above, of a two-chamber system with a communication.

The foregoing theoretical, anatomic, and experimental evidence indicates that the proposed concept is acceptable, so that we may now turn to a consideration of the dynamic effect of the auricular axial plane and the plane of the septal patency on cardiodynamics.

The first year of life is spent almost entirely in a recumbent position. Since the septal defect then lies in a nearly vertical plane, the conditions of the first portion of the model experiment are approached. But with the body in the recumbent position, the right auricle lies somewhat anterior to the left (above), as shown in Fig. 2. One may surmise that this axis is less exaggerated in life, i.e., that the auricular axis is more transverse than is apparent in the sketch, or, that if there is any flow from right to left, it is insufficient to produce cyanosis.

As the upright position is assumed, gravitational flow of blood from the left auricle becomes a certainty, for with that chamber lying cephalad to the right, and with the interatrial septal defect in the floor of the upper chamber, this shunt must function. Filling of the right auricle is accomplished not only by the usual means, but also by the flow-off from the left auricle caused by gravity. The right auricle will dilate in order to accommodate this added load, as will the right ventricle. Eventually, because of the increased flow through it, both chambers of the right side of the heart will hypertrophy. The pulmonary arterial system, which receives an increased volume of blood from the right side of the heart, also dilates. The systemic chambers and vessels, on the other hand, maintain a status quo, or, because they receive less than the usual quantity of blood, undergo regressive changes. This is readily seen in the aorta, which tends to become hypoplastic.

The fundamental "gravitational disposition" of the auricles remains essentially the same, even after the gradual shift of the heart to the so-called "adult position," which is completed between the seventh and tenth years of life.²³ The vicious cycle, therefore, is continuous throughout life, except during the time that the recumbent position is assumed.

If a person with an interauricular septal defect should have one or more attacks of rheumatic fever, with resultant valvular disease, particularly of the mitral valve, the role of this superimposed lesion on cardiodynamics must be considered. The frequent incidence of rheumatic valvulitis in these cases has already been referred to, and, as indicated, is quite common. When an effective mitral stenosis is established, the residual volume of blood that usually causes such profound changes in the left auricle has almost a negligible effect on that chamber. It is obvious that the blood which is prevented from passing to the systemic circuit through the stenotic orifice flows directly into the right auricle, and there merely adds to the increased load on the right side of the heart.

In the light of the foregoing discussion, it is apparent that the heart in Lutembacher's syndrome undergoes essentially the same pathologic changes as the heart which is the seat of an uncomplicated interatrial septal defect. Further, the structural changes in both forms can readily be accounted for by the gravitational disposition of the auricles and plane of the patency between them, without hypothesizing a pressure gradient between the auricles, which, as shown, may be questioned from several standpoints.

SUMMARY

A report of a case of Lutembacher's syndrome (combination of interatrial septal defect and mitral stenosis) is presented. The currently held view of the dynamic changes in such a heart is discussed. It is

pointed out that the fundamental disturbance in dynamics is the same whether or not the septal patency is complicated by a mitral lesion. According to previous investigators, the ultimate development of marked dilatation and hypertrophy of the right auricle and right ventricle, with minor involvement of the left auricle and left ventricle, is caused by shunting of blood through the communication, which in turn results from the fact that the pressure in the left auricle is higher than that in the right. Evidence is presented to show that this explanation is not tenable.

A new concept of the dynamics of interatrial septal defect, based on a correlation between fundamental hydraulic principles and anatomic and experimental considerations, is proposed. It is shown that when two adjoining chambers have a source of constant and equal inflow, a free communication in their common wall, and outflow orifices of equal diameter, the gravitational orientation of the chambers determines their respective sizes, intraluminal pressures, and volume flows. If the chambers are placed one above the other, with the communication in a horizontal plane, the inferior chamber dilates and its outflow trajectory extends beyond that of the upper chamber, which indicates that there is a greater intraluminal pressure in the lowermost chamber.

From an anatomic standpoint, evidence is presented to show that the auricular axis is such that the left auricle occupies a definitely more cephalad position than the right. Further, the plane of the foramen ovale (septal defect) is almost horizontal, and not vertical, as it is commonly represented. With the disposition of the chambers and septal defect in this relationship, filling of the right auricle is accomplished by the usual caval flow, and by a gravitational flow through the communication in the floor of the superiorly placed left auricle. Dilatation of the right auricle results, and, in due time, the right side of the heart shows dilatation and hypertrophy, whereas the left auricle and ventricle, which play almost no role in these events, remain essentially unaffected. The aorta becomes hypoplastic because of the decreased systemic volume of blood. The pulmonary arterial tree, on the other hand, necessarily dilates to accommodate the increased volume of blood in the lesser circuit. The presence of mitral stenosis simply exaggerates the flow differences.

The proposed concept obviates the necessity of postulating a pressure gradient theory to explain the pathologic changes, and offers, instead, a well-correlated explanation of the entire progression of events which are associated with an interatrial septal defect.

I wish to express my appreciation to Dr. G. Fahr, Chief of Medicine, Minneapolis General Hospital; and Dr. L. N. Katz, Director of Cardiovascular Research, Michael Reese Hospital, Chicago, for their criticisms and suggestions in the preparation of this report.

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THE EFFECT OF CHRONIC LEAD POISONING ON ARTERIAL BLOOD PRESSURE IN DOGS

PAUL J. FOUTS, M.D., AND IRVINE H. PAGE, M.D.
INDIANAPOLIS, IND.

THE belief that chronic lead poisoning leads to arterial hypertension extends deep into the annals of clinical medicine, but the evidence on which it is based is unconvincing. Lead intoxication has been studied in a number of animal species, but rarely has the blood pressure been measured, and then the method employed has not been the best.

Since little is known of the effect of lead intoxication on arterial blood pressure, we thought it desirable to make a prolonged study of the effect on mean arterial pressure of feeding two dogs diets in which the amount of lead was accurately measured.

METHODS

Arterial pressure was measured by direct femoral arterial puncture with a 20-gauge needle and a recording mercury manometer. Weekly erythrocyte and leucocyte counts and hemoglobin and urinary protein determinations were made. The lead, in the form of aqueous lead acetate solution, was administered by means of a short esophageal tube. The amount was calculated as metallic lead. The diet consisted of dog biscuits.

PROTOCOLS

A one-year-old female dog, weighing 9.3 kilograms, began receiving lead acetate December 31, 1937. The erythrocyte count was 7.19 millions, the hemoglobin, 111 per cent, and the leucocyte count, 15,000 (Fig. 1). The amount of lead was gradually increased until loss of appetite and weight, bloody diarrhea, and a lead line developed. It was then discontinued for a week or more until the acute symptoms and signs receded. It was necessary to discontinue lead administration on four occasions.

It is of interest that, during these four attacks of acute lead poisoning, anemia did not develop nor did an increase in reticulocytes occur. Progressively greater amounts of lead were required to produce each succeeding acute attack. After 34 months of lead administration the dog weighed 8.5 kilograms, the erythrocyte count was 6.9 millions, and the hemoglobin was 95 per cent.

Evidence of irritation of the kidneys was not found. At no time did the urine contain abnormal amounts of protein. Since the blood pressure was normal after 34 months of lead administration, it seemed desirable to try to elevate the pressure by removing normal renal tissue. Unilateral nephrectomy was therefore performed, but still no rise in pressure occurred. A rapid decrease in weight was observed, and 27 days later severe lead poisoning developed. Marked encephalitis accompanied this attack. The dog was in such poor condition that she was sacrificed on December 31, 1940. During the final illness the erythrocyte count decreased to 5.97

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital.
Received for publication March 13, 1942.

millions and the hemoglobin to 60 per cent; this was associated with a rise of reticulocytes to 6.2 per cent on the day of death. There had been no reticulocytosis prior to the final attack. This suggests that the variations in the erythrocyte count resulted from differences in hydration of the dog, rather than alterations in production and destruction. Autopsy showed the usual morbid changes which are induced by lead intoxication.

This dog received a total of 32.5 grams of lead over a period of three years.

A second dog was studied for a much shorter time because it died during the second attack of acute lead poisoning after a total of 1.9 grams of lead had been administered. No abnormal changes in arterial pressure were observed.

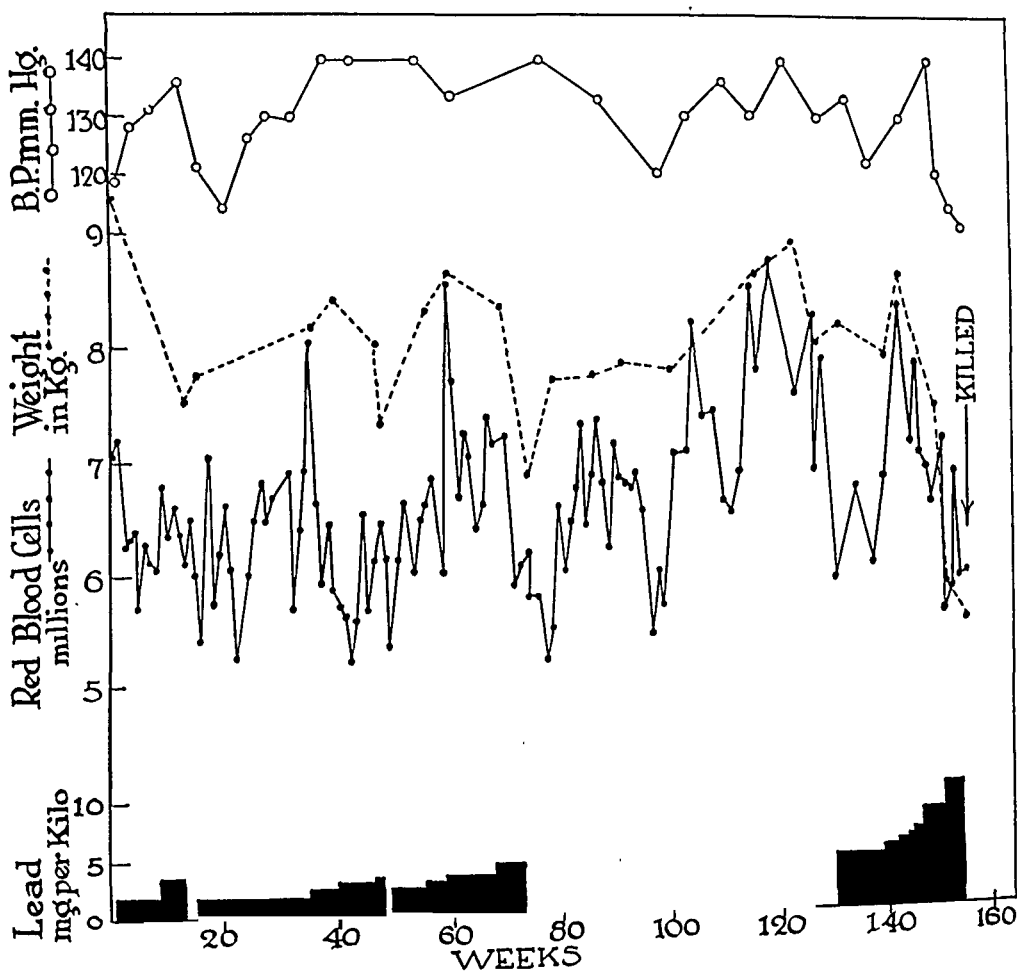


Fig. 1.

DISCUSSION

Despite prolonged (160 weeks) administration of large amounts (32.5 grams) of lead to a dog, no significant change in mean arterial pressure occurred. The dog survived four attacks of acute lead poisoning and died during the fifth, indicating the severity of the treatment. Weight loss and bloody diarrhea occurred when the amount of lead was progressively increased; this culminated in an acute attack, but recovery soon took place when the administration of lead was discontinued. At the height of the first four acute attacks there was no demonstrable

anemia. However, there was a temporary decrease in the erythrocyte count and hemoglobin percentage after the attacks; this suggested that concentration during the attacks masked slight anemia.

Arterial hypertension can be produced in dogs with ease by other methods, and therefore there is no reason to suppose that it would not occur after lead administration if this substance were capable of producing it. Since the animal received lead in large amounts for about one-third of its life span, time for the development of hypertension was certainly adequate. We therefore conclude that lead, under the experimental conditions which were used by us, does not produce arterial hypertension in dogs.

It was stated before that careful reading of the literature on the possible relationship between chronic lead poisoning and hypertension in human beings leads to the conviction that such a relationship has not been demonstrated. The problem in human beings needs reinvestigation.

CONCLUSION

Administering lead to dogs over long periods of time and in large amounts does not produce arterial hypertension.

THE SEGMENTAL AND AGEING VARIATIONS OF REACTIVE HYPEREMIA IN HUMAN SKIN*

JOSEPH R. DiPALMA, M.D., AND FRANCES I. FOSTER, B.S.
BROOKLYN, N. Y.

THAT the ability of the skin to undergo reactive hyperemia varies at different segmental levels has been a common observation.^{1, 2} With the advent of a simple, reliable method which is capable of quantitating the threshold of reactive hyperemia to local ischemia, it is now possible to map by serial segments the capacity of the skin to respond in this regard.³ Furthermore, data obtained upon selected subjects in proper age groups should reveal significant changes, if any, in the senescence of the smaller blood vessels of the skin.

Such a study, showing topographic and age variations of reactive hyperemia in the skin, ought to be of theoretical interest and practical importance. It should reveal the relationship between the responsiveness of the smallest blood vessels and the concentration of oxygenated and reduced hemoglobin in different cutaneous body segments, as recently measured by Edwards and Duntley.⁴ The role of local skin temperature in the control of small dermal blood vessel responses might be further elucidated.

In practice, such data might serve as a base line of the capacity for reactive hyperemia of the small dermal vessels in different body segments. The uses of this would be many. It might aid in estimating the proper strength of drugs to be applied to the skin in various body areas; in the interpretation of the local responses in allergy testing; and as a means of comparison in the study of the smaller skin circulation in cases of organic and functional closure of blood vessels.

METHODS AND PROCEDURES

The methods used in these studies have been described previously.³ In that paper it was shown that the reactive hyperemia which results from local ischemia produced by applying weights to the skin can be quantitated. Furthermore, the threshold hyperemia response which was obtained followed the postulates of Lewis¹ concerning the smallest blood vessels of the skin, and therefore was a measure of their responses rather than those of the arterioles. Over 500 determinations were made on about 100 subjects. It was shown that the threshold response did not vary in the same subject when it was ascertained on the same day under conditions of ordinary activity, environment, and diet. There was a seasonal change in the threshold, however, which correlated with the prevailing outside temperature. It was demonstrated that the threshold varied reliably with reflex

From the Department of Physiology and Pharmacology, and the Department of Medicine, Long Island College of Medicine.

Received for publication Feb. 23, 1942.

*Aided by grants from the Josiah Macy, Jr., Foundation, and the Committee on Endocrinology, National Research Council.

heat, and with local heat and cold in a manner consonant with known concepts of blood vessel responses. The local and remote changes in the threshold consequent to acute and prolonged stasis were elucidated. It is therefore felt that the method used in this study is a reliable criterion of the hyperemia responses of the smallest dermal blood vessels of the human skin. A brief description of the technique will now suffice.

To the bottom of a 500-gram lead weight is attached a smooth rubber ring whose lower surface is five square centimeters in area. This weighted ring, which obviously has a weight loading of 100 grams per square centimeter, can be applied to practically any surface of the body. In practice the following procedure was adopted. The weight is quickly and deftly applied to the selected area of skin, and held balanced by the tip of the forefinger, exerting as little additional pressure as possible. After a certain time, measured in seconds by a stopwatch, the weight is quickly removed and the resulting reactive hyperemia is carefully observed. Various stimulation times are tried. The period of stimulation which is just sufficient to produce a hyperemic ring of even intensity and texture, with discrete edges, is known as the *threshold time*. It has been found that the average stimulation time for such a response in the skin of the forearm is about 10 to 15 seconds in midsummer and about 70 to 80 seconds in midwinter. When the stimulation time is less than threshold, a mottled, uneven ring results; when it is more than the threshold time, a more intense hyperemic ring develops, with an arteriolar flare. At the threshold, the time in seconds required for the hyperemic ring to fade to the color of the surrounding skin is taken. This is known as the *clearing time*, and is directly related to the rate of blood flow in the skin.* All observations are made with the aid of a blue, or daylight, maida bulb. The environmental temperature was usually 75° F.

All the subjects for this investigation were patients on the wards of Kings County Hospital, Long Island College of Medicine Division. All were males, with the exception of subject A. D. Particular care was taken to ascertain that they were normal physically and mentally. Nearly all of them had entered the hospital for a minor elective surgical operation, such as *herniorrhaphy* or *hemorrhoidectomy*. Two subjects, H. B. and A. D., had completely recovered from a minor attack of rheumatic fever. No subject was used who had a history of skin rashes, allergic disorders, or peripheral vascular disease. Subjects in the fourth decade, or over, were tested oscillometrically for evidence of organic closure of the vessels of the extremities.

Following the recommendations of Purves-Stewart,⁶ with modifications, the surface of the human body was considered as a map with no anteroposterior dimension, and the limbs were placed in a position analogous to that of the alligator (see Fig. 1). It will be observed that in this position the nerve distribution of the limbs follows the serial order of the somatic segments. This greatly facilitates visualization and interpretation of the data.

RESULTS

Individual Gradient of Reactive Hyperemia.—The thresholds and clearing times were ascertained in fourteen dorsal and fifteen ventral positions, covering all the cutaneous branches of nerve segments from the ophthalmic division of the fifth cranial nerve to the fifth sacral nerve (Fig. 1). Despite individual variations, certain definite trends were found in the trunk of a normal person in the third decade of life.*

*In this investigation, seasonal changes in reactive hyperemia in the skin, as previously demonstrated, do not enter as a significant factor, since practically all the subjects were studied at the same time of the year, namely, September and October, 1941.

TABLE

THE SEGMENTAL THRESHOLDS AND CLEARING TIMES OF FOURTEEN REPRESENTATIVE SUBJECTS,
THE MOST MARKED CHANGES ARE

REGION OF BODY	B. S. Age=2		A. D. Age=9		D. Z. Age=12		H. B. Age=13		D. G. Age=24		L. S. Age=26		A. M. Age=29	
	Th.*	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.
FACE														
Forehead	15	45	15	40	15	20	20	30	13	23	23	40	13	25
Cheek	28	40	18	33	13	30	15	27	18	27	8	20	33	43
NECK														
Dorsal	30	31	28	40	23	38	13	19	15	30	23	35	35	30
Ventral			20	25	35	40	25	25	40	25	15	50		
TRUNK														
Dorsal														
Scapular	30	31	28	30	38	35	23	25	43	40	23	50	38	35
Lower chest	33	38	28	25	33	20	25	30	48	50	23	25	33	28
Lumbar	25	30	30	23	33	25	28	30	48	20	28	30	33	18
Buttocks	13	14	18	15	12	12	13	15	23	20	18	20	13	18
Ventral														
Upper chest	35	23	30	110	28	45	55	55	58	28	38	50	35	30
Lower chest	35	23	35	105	48	29	45	35	68	38	28	33	30	25
Upper abdomen	38	68	40	25	55	70	45	35	70	30	33	25	35	25
Lower abdomen	38	95	33	15			45	35	70	30	40	25	40	26
UPPER EXTREM- ITY														
Dorsal														
Axillary (Del- toid)	25	25	30	25	35	50			20	20	30	75	28	33
Brachium	28	28	33	45	48	65	25	35	70	55	35	85	40	30
Antibrachium	33	60	38	73	43	45	35	40	73		58		43	35
Hand	33	40	33	80	35	60	18	36	63	80	58	70	43	40
Ventral														
Brachium	33	32	33	83	45	70	45	43	63	90	38	80	48	45
Antibrachium	33	42	38	40	45	70	38	40	63	80	58	78	43	45
Palm	28	28	28	30	38	60	25	40	28	50	38	55	33	28
LOWER EXTREM- ITY														
Dorsal														
Upper thigh			40	70	60	65					53	55		
Lower thigh	33	52	48	85	60	65	50	43			78	90	120	90
Upper leg	38	54	45	48	73	87	60	25			98	95	120	110
Lower leg			55	93	70	140	90	65			128	130	110	250
Foot	35	95	70	100	80	160	110	80	120	225	110	600	85	110
Ventral														
Upper thigh	33	88			45	50			75	55	73	120		
Lower thigh					38	35	50	32	85	80	78	150	78	60
Upper leg	28	49			63	73	55	53	93	60	80	220	165	160
Lower leg					58	55	80	32	120	140	115	200	175	200
Sole (Plantar)	25	50	38	70	45	45	28	36	70	55	50	480	60	94

*Th. = threshold time in seconds.
C.T. = clearing time in seconds.

I

SHOWING THE EFFECTS OF ADVANCING AGE UPON THE SEGMENTAL GRADIENTS. NOTE THAT LIMITED TO THE LOWER EXTREMITIES

P. B. Age=30		T. S. Age=42		L. E. Age=47		A. Mac. Age=51		D. R. Age=51		V. C. Age=72		W. W. Age=80	
Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.
43	55	23	55	35	60	38	60	18	25	13	25	18	28
43	65	30	42	35	86	38	60	23	50	15	25	110	75
48	60	75	95	35	60	68	85	40	45	43	30	63	35
30	37	28	40			38	50	25	62	23	23	48	40
38	35	65	110	55	70	65	125	43	45	40	35	28	25
40	23	60	75	45	70	65	135	38	35	45	38	38	35
40	20	50	30	75	85	58	35	48	30	30	20	43	32
28	13	28	25	35	43			38	20	25	13	9	20
60	80	63	110	45	90	70	42	48	51	48	35	28	45
40	32	65	100	35	75	60	95	48	47	48	45	23	35
50	20	55	180	35	40	73	22	65	60	48	25	23	31
48	22	55	180	35	40			80	75	48	25	23	31
		55	115	40	41	55	70	45	45	48	30	43	35
43	40	55	100	80	95	70	105	53	53	50	40	40	45
50		68	70	85	100	58	120	100	105	98	75	33	40
		60	90	120	155	68	100	110	110	58	90	38	48
38	66	48	100	38	104	68	100	48	90	73	65	48	72
38	66	43	100	38	110	50	75	63	100	75	80	43	45
40	80	35	48	100	120	58	120	38	55	50	55	38	20
45	75	75	90	100	125			55	55	83	100	73	65
60	30	65	135	100	125	180	120	75	85	83	105	68	50
55	40	95	170	110	105	145	145	110	200	93	75	240	300
70	100	85	195	110	130	110	350	100	300	98	90	300	420
83	120	85	180	90	95	110	250	100	600+	105	200	300	600+
55	80	103	115	100	119	120	125	50	40			68	25
33	25	83	125	100	122	135	110	75	75			63	40
58	70	110	130	100	130	240	150	110	200	105	180	300	300
58	80	110		80	107	180	180	120	240	105	330	240	300
28	100	55	75	100	100	50	100	110	300	48	45		

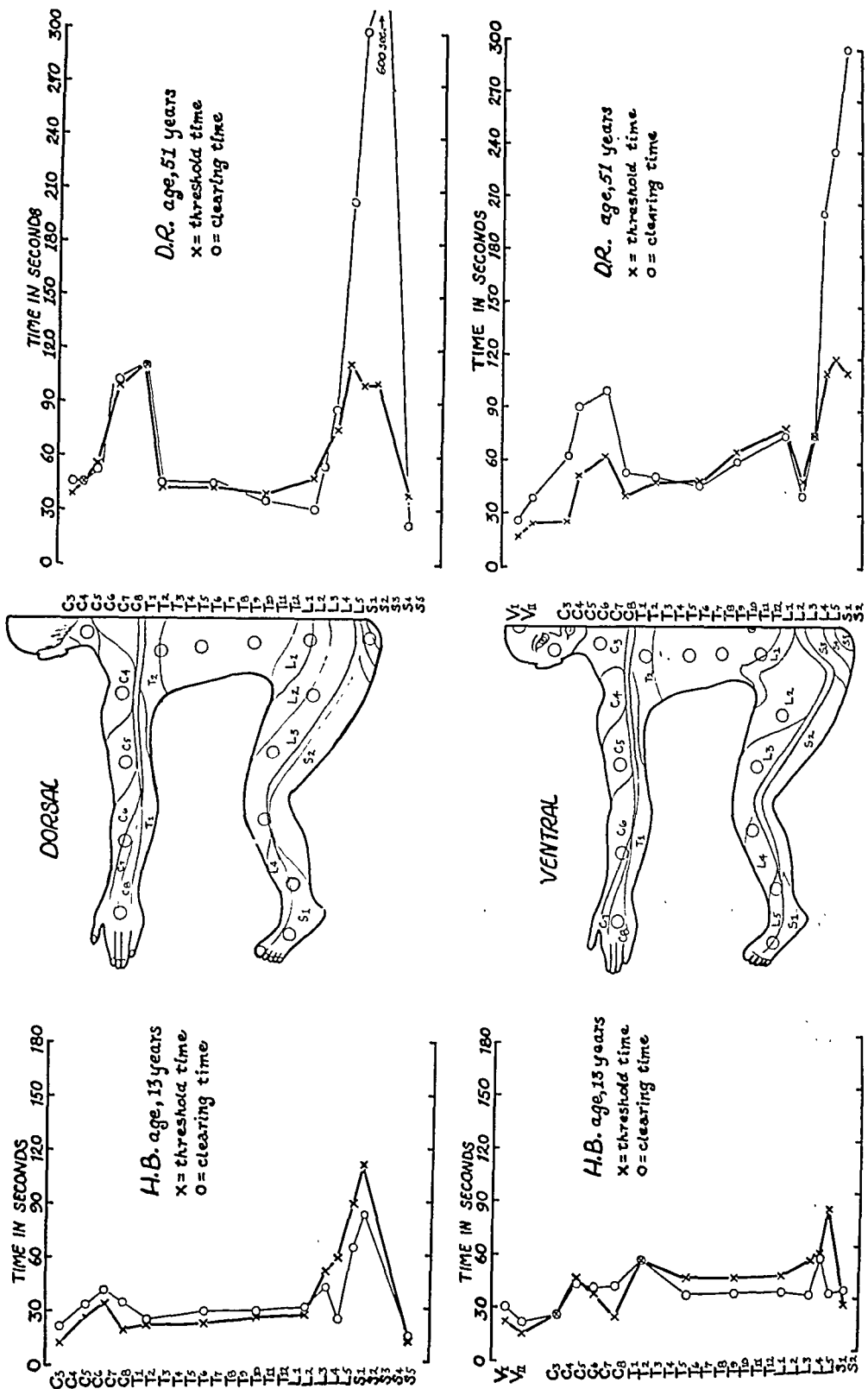


Fig. 1.—Relationship of various nerve segments and their respective thresholds (crosses) and clearing times (circles). Both dorsal and ventral gradients are illustrated in a subject in the second decade and one in the sixth decade of life. The circles on the figures correspond approximately to the areas of application of the weighted ring.

It was found that there is a slight but constant positive gradient in the thresholds and clearing times as one passes from the highest to the lowest nerve segments. Thus, in subject A. M. (Table I) the threshold in the flush areas of the body (face, neck, and upper part of the chest) was about 33 seconds; over the lower part of the abdomen it rose to 40 seconds. The clearing times closely parallel the threshold times. Close scrutiny of Table I and Fig. 1 will reveal that the gradient in the trunk is generally more marked on the ventral surface. One constant feature in all subjects was a very low threshold over the buttocks (sacral 4-5), which compared favorably with the most reactive parts of the body, such as the face and neck.

In the extremities, as might be expected, there is a very marked gradient in thresholds and clearing times. Thus, in subject A. M. (Table I) the threshold for the ventral surface of the forearm was 43 seconds and the clearing time was 35 seconds, whereas, on the ventral surface of the lower part of the leg, the threshold was 175 seconds and the clearing time 200 seconds. The more marked rise of clearing time in this latter instance signifies that there was a slowing of the cutaneous blood flow in this region. This will be more fully discussed later. Generally, the threshold was somewhat lower and the clearing time longer in the palm and the sole, as in this subject. Variations in this respect are attributable to the thickness of the stratum corneum in this area, which interfered with the reading of the reactions.

The Variations of Threshold With Age.—By selecting 14 representative subjects, grouped roughly into decades, it was possible to study any age variations that might be present in the thresholds and clearing times. It will be seen by glancing from left to right in Table I that there are no significant ageing differences in so far as the flush areas of the body or the trunk itself are concerned. In the extremities, however, there is a gradually increasing threshold, and this is directly related to age. This is most marked and constant in the lower extremities. Thus, in subject W. W., who was an unusually hale and hearty person of eighty years, whose habit it was to walk two miles each day, the threshold showed a remarkable rise to 300 seconds and the clearing time to 600 seconds in the foot. Study of Table I reveals that this rise in the lower extremities is constant in persons in the second decade of life or older. Furthermore, with some exceptions, the rise in threshold seems to be roughly proportional to the age of the subject. The even greater rise of clearing time in this area, it may be noted, betokens a local slowing of blood flow. Another striking feature of the results was the absence of a gradient in the youngest subjects, B. S. and A. D. (Fig. 2 and Table I). This was particularly pronounced in the former. During the actual course of the determinations there was little difference in the reactions, either qualitatively or quantitatively, no matter which area of the body was studied. This is in marked

contrast to older subjects, in whom gross differences are immediately apparent when one passes from the trunk to the extremities.

Although the number of subjects in each age group is small, it must be remembered that each subject was carefully selected and had a

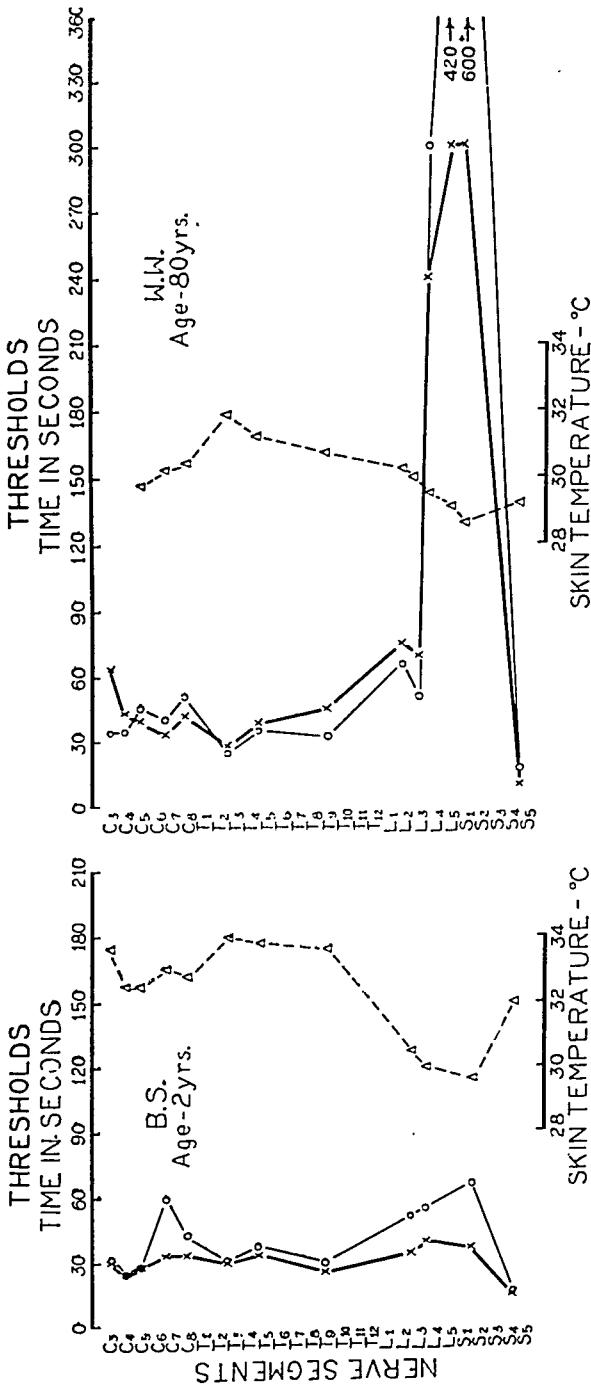


Fig. 2.—Comparison of the gradients of thresholds (crosses) and clearing times (circles) to the corresponding surface temperature gradients (triangles) in a subject in the first decade and one in the ninth decade of life. Only the dorsal surface has been plotted in this diagram. See text for discussion.

total of 29 separate serial determinations of the threshold of reactive hyperemia. Moreover, the fact that the responses in the lower extremities vary with age, whereas those in the face and trunk do not, lends support to the view that the ageing variations which were observed

are actual ones. To narrow the limits of this ageing difference, a study on a much larger group of subjects is contemplated, but restricted to fewer and significant segmental areas.

Surface Temperature and the Segmental Threshold.—In over two-thirds of the subjects, surface temperatures were taken in each area in which the threshold was studied.* Thus, the segmental gradient of surface temperatures could be compared to the segmental threshold. Fig. 2 shows the segmental thresholds and surface temperatures in the youngest and oldest members of the series. It will be seen that there is no exact correlation. In the extremities, as is to be expected, the temperatures are lowest, and it is here that the highest thresholds and clearing times are obtained. The relationship is by no means a linear one, however, especially in the younger subjects. This is surprising, for our own previous studies and those of other investigators have demonstrated that changes in temperature, not only local, but also reflex and environmental, have profound effects upon blood flow and reactive hyperemia in the skin.^{3, 7, 8, 9} There are other factors, however, which must be taken into consideration. The techniques of recording surface temperatures are by no means perfect. The temperatures we obtained agree in general with those of other investigators,^{5, 7} but their studies were unfortunately limited to one age group, usually adults in the third decade of life. Our studies include the very young and the very old, and it is at these ages that the most divergent results are found.

It must also be stressed (as has been pointed out before^{3, 10}) that these vascular reactions are localized to the smallest blood vessels of the skin; namely, the vessels beyond the arterioles. Factors which may ordinarily have demonstrable effects upon the larger vessels may not as markedly influence the responses of these smallest vessels. It is also probable that factors other than temperature are just as important in the local control of the smallest blood vessels.^{1, 3, 10}

The main purpose of the temperature studies reported here is served, however. That is to demonstrate that in different subjects the segmental gradient of reactive hyperemia is not necessarily dependent upon the segmental gradient of surface temperatures. This is clearly demonstrated in Fig. 2. The temperatures also served as an indication that the subject was under standard conditions of arterial tone, and not under an unusual degree of vasoconstriction or vasodilation.

Local Blood Flow and the Segmental Threshold.—The rise of thresholds in the lower extremities requires further explanation. The thought which comes immediately to mind is that the most salient factor in the segmental gradient of reactive hyperemia is local blood flow in the skin.

*A Tycoos Dermatherm was used in some of these determinations, and a Leeds and Northrup Automatic Recording Micromax, with a 30-gauge iron-constantan junction, was used in the rest. Care was taken to secure optimal conditions for the recording of surface temperatures. The room temperature was maintained at 75° F., and the subject, who was lightly clad, was left exposed to room air for one hour.

Repeated observations have shown that dilation of small blood vessels may be elicited even when there is complete stasis in an extremity.¹ It has also been demonstrated that the threshold of reactive hyperemia to local ischemia is not changed by complete stasis, but that the clearing time is very markedly prolonged.³ This is ascribed to the fact that blood flow is essential for removal of the hypothetical "H" substance which is produced by the ischemia.

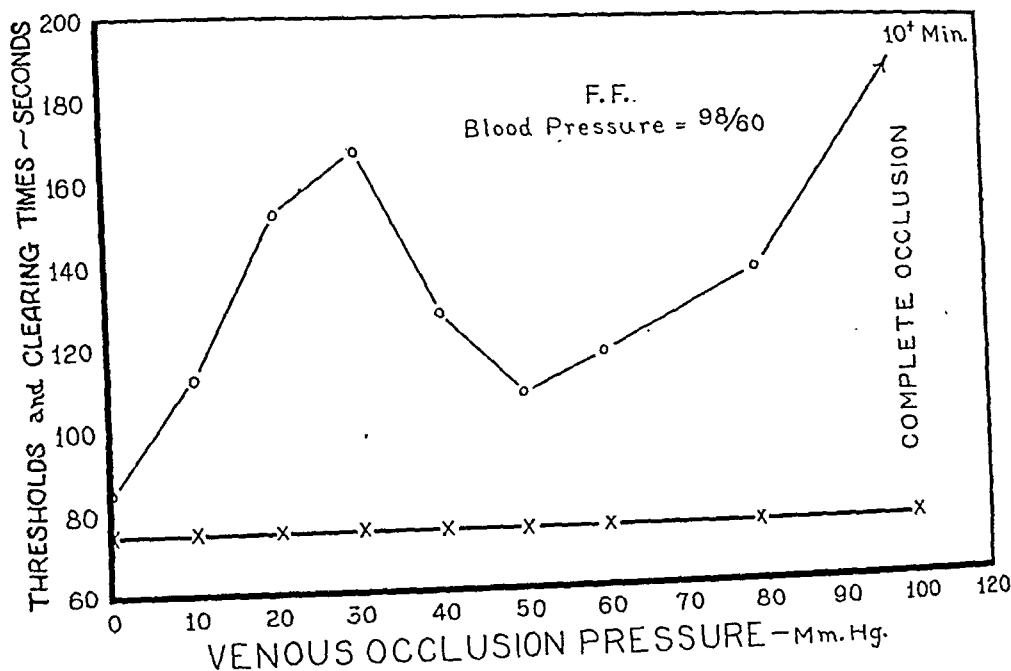


Fig. 3.—Effects of gradually increasing venous occlusion upon the thresholds (crosses) and the clearing times (circles), as ascertained on the skin of the ventral surface of the forearm.

In order to test these observations further, the following experiment was performed several times. Using the skin of the ventral surface of the forearm, the thresholds and clearing times were obtained. By means of a blood pressure apparatus, venous stasis was then produced, and the thresholds and clearing times again determined. This was done at intervals of 10 mm. Hg until complete stasis was attained. Ample time was allowed after determination at a certain pressure to insure complete circulatory recovery of the limb. The results of one such experiment are charted in Fig. 3. There was no change in the threshold time, as was expected. The clearing time, however, rose rapidly to 167 seconds at 30 mm. Hg occlusion pressure. Beyond this pressure there occurred a shortening of clearing time which reached its lowest point, in this instance, at 50 mm. Hg. This point was considerably above the control clearing time. As the occlusion pressure was further increased there was a gradual rise in the clearing time, until, with complete circulatory stasis, the time for the hyperemic rings to clear became infinitely long. It was observed for 10 minutes

in this instance, at which time the hyperemic area was still very pronounced. Presumably the secondary fall in clearing time at 30 mm. Hg was the result of dilation of vessels on the arterial side as part of the mechanism of compensation for the venous stasis. This explanation is supported by the observation of Lewis and Grant¹¹ that *during* the period of venous stasis in a limb the arterial pulse, as recorded by a plethysmograph, increases in volume. It is notable that the clearing time during this secondary fall does not descend to the control level, and therefore blood flow in the smallest skin vessels *during* venous stasis only approaches the normal resting blood flow, and does not exceed it. The contention of Linton, et al.,¹² that the arterial inflow in a limb in which venous obstruction is present actually exceeds the normal resting inflow is therefore not confirmed by these studies.

It seems, therefore, that the long clearing times in the extremities of the aged are the result of a local slowing of blood flow. The high thresholds observed in the same regions cannot be ascribed to this cause, however. Other factors, i.e., nervous, postural, and humoral, undoubtedly contribute to this effect.

DISCUSSION

Anatomic studies of the segmental and age variations in the smallest blood vessels of the skin have been made, but unfortunately they have not included the lower extremities. It has been found that the number of capillaries in the cheek, ear lobe, forearm, and hand does not differ significantly.² In addition, there are no discernible changes with advancing age.¹³ Our studies on the functional responses of these small blood vessels confirm these observations. They add the fact, however, that the most marked gradient is in the lowest nerve segments, and, furthermore, that the ageing effects occur almost exclusively in the lower extremities. Wetzel and Zotterman² also showed that the highly colored regions of the body, such as the cheek, owe this property to a relatively atonic state of the capillaries and venules. It is therefore reasonable to assume that segmental threshold differences in the responses of these small vessels are the result of functional alterations, rather than anatomic ones. A morphologic study of the capillaries in the lower extremities with respect to ageing would be desirable, however.

The excellent studies of Edwards and Duntley⁴ have demonstrated that the ratio of reduced to oxygenated hemoglobin, as ascertained by spectrophotometric analysis of the skin, may vary markedly. The proportion of oxyhemoglobin is highest in the cheek, palm, buttocks, and sole, and increased in the face and upper part of the chest; that of reduced hemoglobin is greatest in the lower part of the abdomen, scrotum, and dorsum of the foot. It is, therefore, obvious from our

studies that the most responsive skin areas correspond closely to the regions which are most rich in oxyhemoglobin, and vice versa. It has also been demonstrated that the sensitivity of the smallest blood vessels is markedly decreased in systemic anoxemia before there are marked changes in blood pressure, pulse rate, and respiratory exchange.¹⁰ The implication is that one of the most important factors which determine the reactivity of these vessels is the degree of oxygenation of the blood they contain.

It is generally maintained (and Abramson, et al.,¹⁴ have recently confirmed this by plethysmographic studies of various portions of the extremities) that the degree of the hyperemic response consequent to deprivation of blood is related to the metabolic needs of the tissues concerned. Also, it is well known that the skin, particularly that of the hand and foot, serves the important function of dissipating heat. Sheard and Williams⁷ have demonstrated that the basal metabolic rate of normal persons is related to the temperature fall in the toes when the extremities are left exposed under standard environmental conditions. Those with the higher basal metabolic rates showed the least temperature fall.

These studies, however, were carried out with methods which measure largely the responses of arterioles (plethysmographic and surface temperature); consequently, the results may not apply directly to the responses of the smallest blood vessels which we have studied. With this difference in mind, certain correlations are indicated. Those areas of the body which are most subject to pressure, and contact with the atmosphere, i.e., the palms, soles, buttocks, cheeks, and therefore incur the greatest metabolic debt, have the most responsive blood vessels and are supplied with the most highly oxygenated blood. On the other hand, the skin of the lower extremities, with the exception of the sole, because of its location, is seldom called upon to bear the weight of the body, either in the erect or the recumbent posture. The surface temperature in these regions is also consistently lower than that of the rest of the body, and it is here that the highest thresholds of the reactive hyperemia which results from local ischemia are found.

SUMMARY AND CONCLUSIONS

By using a method which was previously developed for quantitating the reactive hyperemia which results from local ischemia, it was possible to study this response in serial body segments. Two components are described, namely, a *threshold* and a *clearing time*. Correlations were made with surface temperatures and with age. The following conclusions were reached:

1. There is a positive gradient of reactive hyperemia resulting from local ischemia which is directly related to the nerve segment involved.

The more caudal the nerve segment, the higher the threshold and clearing time. This gradient is slightly more marked on the ventral surface of the body.

2. Certain areas of the body are more responsive than the mean gradient. These include the palm, sole, cheek, and buttocks.

3. The extremities cause sharp peaks in the mean slope of the gradient. This sharp rise in threshold and clearing time is much more marked in the lower extremities.

4. In general, the clearing time, which has been shown to be directly related to blood flow, parallels closely the threshold time. In the lower extremities, however, it may rise to much greater levels than the threshold.

5. Simultaneously conducted segmental temperature studies indicate that, under standard environmental conditions, the segmental gradient of temperature is not the principal factor in the difference in the segmental gradients of reactive hyperemia which are observed in different subjects.

6. With advancing age, the slope of the gradient of the thresholds becomes more inclined. The youngest subjects may show no gradient at all, whereas the most aged show a very steep gradient. This phenomenon is limited largely to the lower extremities. In this regard, age affects the clearing time even more. This is attributed to a normal, marked slowing of local cutaneous blood flow in the extremities of the aged.

7. These observations suggest that any studies on reactive hyperemia in the skin, either in health or in disease, in order to be well founded, must be interpreted in the light of what segmental areas are studied and the ages of the subjects.

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A REACTIVE HYPEREMIA RING TEST IN THE STUDY, EVALUATION, AND PROGNOSIS OF PEDAL LESIONS CAUSED BY ARTERIOSCLEROSIS OBLITERANS AND ARTERIAL EMBOLISM*

JOSEPH R. DiPALMA, M.D., ISRAEL MUSS, M.D.,† AND
FRANCES I. FOSTER, B.S.
NEW YORK, N. Y.

THE immediate object of this investigation was to apply a direct quantitative method, recently developed and studied,^{1, 2} to the evaluation of the skin circulation in obliterative vascular disorders. Kramer and others^{3, 4} have stressed the importance of such studies in peripheral vascular disease, as contrasted to the usual means of evaluating the functional capacity of the larger arteries, such as oscillometry, plethysmographic and roentgenologic studies.

Existing methods which were devised to achieve this are the histamine test, advocated by Starr,⁵ and the intradermal saline wheal test of McClure and Aldrich.⁶ In our experience and that of others,^{3, 4} the histamine wheal test is an efficient and quick means of obtaining a rough idea of the functional capacity of the smaller skin vessels. It frequently falls far short of exact quantitation, however, and suffers from certain other disadvantages. For example, we have noted that people vary in sensitivity to histamine, and, further, that the most intense responses, although delayed, develop in the presence of a greatly diminished dermal blood flow. In addition, this test depends upon the formation of a wheal; this response is not easily reversible, and therefore borders more on the pathologic than on the physiologic. The inherent disadvantages of the intradermal saline wheal test are discussed elsewhere.^{3, 4}

The method used in the experiments to be described has been shown to be a simple, sensitive, and accurate means of quantitating the responses of the smallest vessels of the skin to local circulatory stasis. It requires nothing more in the way of apparatus than a weighted rubber ring, a stop watch, and a daylight Mazda bulb. Individual, seasonal, segmental, and ageing variations have been described. This procedure measures the ability of the smallest blood vessels of the skin to respond by reactive hyperemia to local ischemia, and, by noting the time required for the area to clear, a direct indication of the rate of local blood flow is obtained.^{1, 2}

Department of Physiology and the Department of Medicine, Long Island College of Medicine, Brooklyn, N. Y.

*Aided by grants from the Josiah Macy, Jr., Foundation, and the Committee on Endocrinology, National Research Council.

†From the Peripheral Vascular Disease Clinic, Polyclinic Hospital.

Received for publication Feb. 23, 1942.

The results of such an investigation upon a selected group of patients who had been adequately studied by the usual methods of examination in peripheral vascular disorders should yield information on at least three points. First, it might serve to indicate whether or not the loss of function of the blood vessels in the skin is the result of a change in the capacity of the smallest blood vessels to respond by reactive hyperemia to local ischemia. Second, it might clarify the exact relationship between obliteration of large vascular trunks and slowing of dermal blood flow. Third, it might serve to provide an exact measure of the degree of functional loss of the skin circulation.

METHOD AND PROCEDURES

Upon the morning of examination the patient was asked to rest in bed in the horizontal position for one hour. He was lightly clad and the room temperature was maintained at about 75° F. After a careful history, physical examination with reference to peripheral vascular disease was begun. Careful note of the physical qualities of the skin and nails was made. The presence or absence of the pulses and their strength and volume were ascertained by palpation. A modified Buerger's test^{4, 7} was then done, as follows: The patient's lower extremities were elevated so that the feet were about 18 inches above the level of the heart. He then dorsiflexed and extended his foot about once a second, moving his toes at the same time. The time required for pallor to appear in any part of the foot was then noted. Finally, the patient was asked to hang his feet over the side of the bed in order to ascertain whether rubor would develop. This completed the usual clinical examination.

The laboratory procedures were kept as standard as possible. Oscillometric readings were made by the same person, with the same instrument, throughout. A histamine test was done on nearly every patient, using the technique described by de Takáts,⁸ and the results were recorded according to the recommendations of Kramer.³ A modified Landis-Gibbon test⁹ was done on those patients who seemed to have more symptoms than the degree of their organic occlusion indicated. This was performed as follows: Skin temperatures were taken on the big toe, dorsum of the foot, ankle, mid-leg, and thigh. Short wave diathermy was then applied to the region of the lower part of the spine for 30 minutes, and skin temperatures again taken 15 minutes after the cessation of this treatment.¹⁰ In our experience, this method of securing reflex vasodilation is not as effective as immersing the hands in warm water as originally recommended by Landis and Gibbon. However, the former method is very convenient, and the results are sufficiently exact for the purpose of this investigation.*

The reactive hyperemia ring test was usually done on the day after the above examination, in order to obviate differences which might be caused by the histamine flares. Four areas, corresponding to the usual areas of injection of histamine³ on each limb, were studied. These areas were the lateral aspect of the thigh, just above the knee (L3), the lateral aspect of the leg, just below the knee (L4), the lateral aspect of the ankle (L4, 5), and the dorsum of the foot (L5, S1). These sites also correspond exactly to the areas which were studied previously in ascertaining the segmental gradient of reactive hyperemia in the lower extremities.² This was done so that any abnormal results could be compared to the expected normal gradient in the proper age group. The time needed to make a complete study of both extremities was greatly shortened by the simple expedient of using two, or even three, weights and stop watches, so that several areas could be studied simultaneously.

*Dr. John J. Hauff was most kind in permitting us to use the facilities of the Department of Physiotherapy, Kings County Hospital, for the testing and examination of the patients.

RESULTS

The Type of Patients Studied.—All of the patients whom we studied were thought to have *arteriosclerosis obliterans* of the lower extremities.† In all, 24 representative patients (9 females and 15 males) were subjected to the above-mentioned tests. Of these, 6 females and 9 males were also diabetic. All of the symptoms caused by progressive, obliterative, arterial disease of the lower extremities, from the early incipient lesions to persistent infection, ulceration, and gangrene, were represented.

In Table I these patients are listed, in so far as possible, in the order of increasing degree of obliteration of the vessels of the extremities. This was judged not only by the results of the objective tests, but also by the symptomatology and the extent of the lesions which were present at the time of examination. Inciting and contributory causes had to be considered carefully. Thus, S. S., the first female patient in Table I, had, by all objective methods of study, the most adequate circulation of the group, but she presented one of the most severe pedal lesions, namely, cellulitis of the foot. However, when cognizance was taken of the inciting cause (the removal of an ingrown toe nail) this discrepancy was explained.

Comparison of Oscillometric and Thermometric Readings With the Skin Tests.—As was expected, no exact relationship obtained between the functional capacity of the larger vessels, as measured oscillometrically, and that of the smallest blood vessels, i.e., the capillaries, venules, and small arterioles, as measured in this study. Although the oscillometric reading usually indicates the side on which the arterial lesion is most advanced, it does not give an exact measure of the extent of the functional loss. Several examples of this are listed in Table I. Particularly illustrative are cases R. R. and P. G.; both patients had markedly diminished oscillometric pulsations of the same order, but the former had pregangrenous lesions, whereas the latter had minimal symptoms and lesions. This confirms the observations of many investigators;^{3, 4, 8, 11} it has been attributed to the fact that the oscillometric method alone does not give any indication of the degree of arterial vasoconstriction which may exist at the time of examination. Moreover, the collateral circulation which develops after obliteration of the larger arterial trunks ordinarily does not register oscillometrically. Therefore, to obviate at least the former factor, it was considered desirable to make thermometric studies of the effects of indirect application of heat (modified Landis-Gibbon test). The results, which are summarized in Table I, show that not one of the patients had any significant degree of arterial vasoconstriction superimposed upon his vascular disease. As has been

†These patients were selected from the various services of the Long Island College of Medicine, Kings County Hospital.

TABLE

CASES OF ARTERIOSCLEROSIS OBLITERANS, SHOWING THE RELATIONSHIP OF TESTS WHICH
THOSE WHICH MEASURE THE FUNCTION OF THE SKIN CIRCUL

SUBJECT	AGE	OSCILLOMETRIC READINGS			HISTAMINE TEST*	SKIN TEMPERATURE
		THIGH	LEG	FOOT		
<i>Females</i> S. S. (D.M.)	58	Excellent pulsations by palpation			(R) Good in all parts. (L) Good in all parts.	(R) Increase in big toe from 29.8° C. to 31.6° C. (L) Sl. increase in big toe from 26.8° C. to 28.0° C.
I. L.	36	(R) 3½	3½	0	(R) Mod. delay in ft.; sl. delay in ank., leg and thigh. (L) Sl. delay in ft., ank. and leg; good in thigh.	(R) No change in big toe—27.0° C. to 27.3° C. (L) No change in big toe—27.5° C. to 27.3° C.
S. P. (R.H.D. + A.F.)	48	(R) S.P.	0	0	(R) Sl. delay in ft. and ank.; good in leg and thigh. (L) Mod. delay in ft.; sl. delay in ank.; good in leg and thigh.	(R) Increase in big toe from 27.5° C. to 29.8° C. (L) Increase in big toe from 27.4° C. to 31.1° C.
R. S. (D.M.)	54	(R) ½	0	0	(R) Good in all parts. (L) Sl. delay in ft.; good in all other parts.	(Not done)
M. F.	74	(R) 1	0	0	(R) Marked delay in ft., ank. and leg; good in thigh. (L) Sl. delay in ft.; good in ank., leg and thigh.	(R) Skin temp. of big toe = 27.5° C. (L) Skin temp. of big toe = 30.5° C.
S. H. (D.M.)	64	(R) 1	¼	0	(R) Mod. delay in leg; sl. delay in ft. and ank.; good in thigh. (L) Sl. delay in ft., ank. and leg; good in thigh.	(R) Increase in big toe from 24.7° C. to 29.8° C. (L) Sl. increase in big toe from 26.7° C. to 28.0° C.
M. K. (D.M.)	68	(R) 2	¾	0	(R) Sl. delay in ank. and leg; good in ft. and thigh. (L) Good in all parts.	(R) No change in big toe—30.3° C. to 30.8° C. (L) No change in big toe—30.2° C. to 30.8° C.
R. R. (D.M. + H.C.V.D.)	75	(R) 2	¾	S.P.	(R) Marked delay in ft.; sl. delay in ank.; good in leg and thigh. (L) Mod. delay in ft., ank. and leg; good in thigh.	(R) Increase in big toe from 27.5° C. to 30.5° C. (L) No change in big toe—27.6° to 27.3° C.

*For explanation of notations of the histamine test see text.

†Th. = Threshold in seconds.

‡C. T. = Clearing time in seconds.

°S.P. = Scarcely perceptible.

D. M. = Diabetes mellitus.

A. F. = Auricular fibrillation.

R. H. D. = Rheumatic heart disease.

H. C. V. D. = Hypertensive cardiovascular disease.

I

MEASURE THE FUNCTION OF THE LARGER VESSELS (OSCHLOMETRY AND THERMOMETRY), AND LATION (HISTAMINE AND REACTIVE HYPEREMIA RING TESTS).

REACTIVE HYPEREMIA RING TEST								PERIOD OF SYMPTOMS	LESION	THERAPY
THIGH		LEG		ANKLE		FOOT				
TH.	C. T.	TH.	C. T.	TH.	C. T.	TH.	C. T.			
(R) 70	50	78	105	78	125	58	155	Cellulitis in left ft. following removal of ingrown toe nail 3 mo. before	Atrophy of skin and nails. Big toe of left foot is hot and red.	Ind. short wave to spine. Intermit. venous occlusion.
(L) 73	75	75	105	73	120	48	90			
(R) 78	55	68	100	63	163	83	155	Coldness of ft. for 1 yr.	Sl. dryness and scaling of skin. Pallor on elevation and sl. rubor on dependency.	Ind. short wave to spine.
(L) 70	55	68	130	68	140	78	110			
(R) 50	75	68	130	85	145	110	200	Acute onset of pain in rt. ft. for 2 wk.	Scaly skin. Pallor in rt. ft. on elevation.	Ind. short wave to spine. Papaverine.
(L) 58	63	63	130	73	155	98	135			
(R) 58	80	58	80	68	220	78	200	Pain in left calf for 5 mo.	Pallor on elevation and rubor on dependency.	Discharged.
(L) 63	80	75	145	98	250	118	275			
(R) 68	18	100	80	100	1800+	65	420	Pain and swelling of rt. ft. for 1 yr.	Red, swollen rt. big toe with sl. ulceration. Atrophy of rt. leg muscle.	Referred to surgery.
(L) 68	40	85	80	95	570	115	180			
(R) 75	65	75	90	75	190	105	300	Intermittent claudication of left leg for 7 mo.	Atrophy of skin and nails.	Ind. short wave to spine.
(L) 75	55	75	100	85	300	135	900			
(R) 65	90	78	120	75	250	110	900	Nocturnal pain for 1 yr. Also intermittent claudication	Atrophy of skin and nails. Rubor of ft. at heart level.	Ind. short wave to spine. Intermit. venous occlusion.
(L) 68	70	75	145	68	600	110	840			
(R) 65	70	65	65	75	1800	110	2400	Intermittent claudication for 2 yr. infection of left heel for 2 mo.	Cellulitis of left ft.	Conservative treatment.
(L) 85	100	85	900	85	3000	95	2880			

TABLE I

SUBJECT	AGE	OSCILLOMETRIC READINGS			HISTAMINE TEST*	SKIN TEMPERATURE
		THIGH	LEG	FOOT		
M. P. (D.M.)	76	(Not done)			(R) Marked delay in lower ft. and ank.; sl. delay in upper ft., leg and lower thigh; good in upper thigh. (L) Amputated.	(R) No change in big toe—28.5° to 28.8° C. (L) Amputated.
<i>Males</i> A. L. (D.M.)	50	(R) 3	1½	0	(R) Sl. delay in ft. and ank.; good in leg and thigh. (L) Marked delay in ank.; sl. delay in ft.; good in leg and thigh.	(R) No change in big toe—26.6° C. to 26.5° C. (L) No change in big toe—26.6° C. to 26.8° C.
M. T.	62	(R) 5	7	½	(Not done)	(R) Increase in big toe from 28.5° C. to 30.5° C. (L) Increase in big toe from 24.9° C. to 29.8° C.
N. L.	63	(R) ½	S.P.	0	(R) Marked delay in ft.; mod. delay in leg; sl. delay in ank. and thigh. (L) Sl. delay in ft. and leg; good in ank. and thigh.	(Not done)
J. S. (D.M.)	66	(Not done)			(R) Mod. delay in ft.; sl. delay in ank.; good in leg and thigh. (L) Good in all parts.	(R) Increase in big toe from 26.7° C. to 32.0° C. (L) Increase in big toe from 27.6° C. to 30.5° C.
P. G. (D.M.)	59	(R) ½	0	0	(R) Marked delay in ft. and ank.; Mod. delay in leg; good in thigh. (L) Marked delay in ft.; sl. delay in ank.; good in leg and thigh.	(R) Sl. increase in big toe from 28.7° C. to 29.8° C. (L) Sl. increase in big toe from 29.1° C. to 29.8° C.
S. M. (D.M.)	61	(R) ¾	⅓	0	(R) Sl. delay in all parts. (L) Sl. delay in all parts.	(R) Increase in big toe from 28.3° C. to 30.5° C. (L) Sl. increase in big toe from 30.2° C. to 31.1° C.
M. L. (D.M.) + Lues)	69	(R) 6½	3	0	(R) Marked delay in ft.; sl. delay in leg; good in ank. and thigh. (L) Marked delay in ank. and leg; mod. delay in ft.; good in thigh.	(R) Skin temp. of big toe = 25.1° C. (L) Skin temp. of big toe = 26.0° C.

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REACTIVE HYPEREMIA RING TEST†								PERIOD OF SYMPTOMS	LESION	THERAPY	
THIGH		LEG		ANKLE		FOOT					
TH.	C.T.	TH.	C.T.	TH.	C.T.	TH.	C.T.				
(R)	65	50	85	150	95	900	110	3600	Gangrene and infection of ft. for 1 yr.	Amputation at left mid-thigh. Punched out ulcer between 3rd and 4th toes of rt. ft.	Referred to surgery.
(L)	Amputated										
(R)	68	55	78	90	78	250	95	200	Pain in left knee and calf for 1 yr.	Sl. atrophy of skin and nails. No lesions.	Discharged.
(L)	68	80	78	165	78	900	88	270			
(R)	73	70	78	60	65	200	85	500	Intermittent claudication for 1 mo.	Atrophy of skin and nails. Patchy arteritis and arteritis of 3 toes on left ft.	Ind. short wave to spine. Intermitt. venous occlusion.
(L)	75	90	80	85	75	200	90	210			
(R)	78	55	83	200	88	780	98	210	Coldness of ft. Intermittent claudication for 10 mo.	Atrophy of skin and nails.	Ind. short wave to spine.
(L)	83	125	93	385	93	480	98	440			
(R)	75	65	88	150	120	480	75	900	Inability to use rt. leg for 1 mo. due to intense pain on walking	Healed ulcer on rt. ft. Atrophy of rt. leg; rt. ft. red and swollen.	Ind. short wave to spine. Intermitt. venous occlusion.
(L)	83	100	78	100	78	900	88	200			
(R)	85	100	95	190	95	145	88	360	Intermittent claudication for 6 yr.	Sl. atrophy of skin and nails. No lesions.	Intermitt. venous occlusion. Ind. short wave to spine.
(L)	75	55	98	135	95	230	98	900			
(R)	93	150	95	230	120	1200	155	900	Intermittent claudication for 6 yr. Infection of rt. big toe for 1 yr.	Infection of rt. big toe; healed.	Ind. short wave to spine.
(L)	85	90	95	385	90	450	110	365			
(R)	70	160	70	240	70	210	95	510	Intermittent claudication for 6 mo. Pain in feet on walking.	Atrophy of skin and nails.	Ind. short wave to spine.
(L)	63	510	65	240	80	900	90	900			

TABLE I

SUBJECT	AGE	OSCILLOMETRIC READINGS			HISTAMINE TEST*	SKIN TEMPERATURE
		THIGH	LEG	FOOT		
F. D. (D.M.)	61	(R) 2	$\frac{1}{4}$	S.P.	(R) Mod. delay in ank. and leg; sl. delay in ft.; good in thigh.	(R) No change in big toe—28.0° C. to 26.6° C.
		(L) 2 $\frac{1}{2}$	$\frac{1}{4}$	S.P.	(L) Mod. delay in ank. and leg; sl. delay in ft. and thigh.	(L) Increase in big toe from 25.5° C. to 27.4° C.
S. S. (D.M.)	53	(R) 1 $\frac{1}{4}$	1 $\frac{1}{8}$	0	(R) Sl. delay in ft. and ank.; good in leg and thigh.	(R) Skin temp. of big toe = 24.1° C.
		(L) $\frac{1}{4}$	$\frac{1}{8}$	0	(L) Mod. delay in ft.; marked delay in ank.; good in leg and thigh.	(L) Skin temp. of big toe = 26.6° C.
H. S.	65	(R) 8	6 $\frac{1}{2}$	$\frac{1}{8}$	(Not done)	(R) Skin temp. of big toe = 30.5° C.
		(L) 5	$\frac{1}{2}$	0		(L) Skin temp. of big toe = 28.3° C.
T. S. (D.M.)	68	(R) 3	3	0	(R) Sl. delay in ft., ank. and leg; good in thigh.	(R) Sl. increase in big toe from 22.8° C. to 23.6° C.
		(L) $\frac{1}{2}$	S.P.	0	(L) Mod. delay in ft. and ank.; good in leg and thigh.	(L) Sl. increase in big toe from 24.0° C. to 25.6° C.
B. S.	67	(R) $\frac{1}{2}$	$\frac{1}{4}$	0	(R) Marked delay in ank.; mod. delay in ft. and leg; sl. delay in thigh.	(R) Skin temp. of big toe = 28.9° C.
		(L) 1 $\frac{1}{2}$	1	0	(L) Mod. delay in ft.; sl. delay in ank., leg and thigh.	(L) Skin temp. of big toe = 28.4° C.
M. S. (D.M.)	69	(R) 9	6	$\frac{1}{4}$	(R) Sl. delay in ank. and ft.; good in leg and thigh.	(R) No change in big toe—27.4° C. to 26.1° C.
		(L) 6	3	$\frac{1}{8}$	(L) Sl. delay in ank.; good in ft., leg and thigh.	(L) No change in big toe—28.7° C. to 27.7° C.
A. W.	35	(R) 5 $\frac{1}{2}$	9	$\frac{1}{4}$	(Not done)	(R) Skin temp. of big toe = 31.4° C.
		(L) 2 $\frac{1}{2}$	1	0		(L) Skin temp. of big toe = 31.0° C.
N. L.	74	(R) 2	0	0	(R) Marked delay from ft. up to knee; good in thigh.	(R) Sl. increase in big toe from 26.7° C. to 28.0° C.
		(L) 2 $\frac{1}{2}$	1	0	(L) (Not done)	(L) No change in big toe—26.9° C. to 26.5° C.

—CONT'D

REACTIVE HYPEREMIA RING TEST†								PERIOD OF SYMPTOMS	LESION	THERAPY	
THIGH		LEG		ANKLE		FOOT					
TH.	C.T.	TH.	C.T.	TH.	C.T.	TH.	C.T.				
(R)	85	95	95	350	68	1200+	95	1020+	Intermittent claudication for 1 yr. Nocturnal pain for 2 mo.	(R) Rose spots over dorsum of ft. (L) Gangrene of 4th and 5th toes. Secondary infection.	Amputation of left leg.
(L)	70	90	70	290	83	2400+	65	330			
(R)	68	50	70	120	73	900	88	2400	Intermittent claudication for 1 yr.	Small ulcers on both legs. Pregangrenous appearance of left big toe.	Intermit. venous occlusion. Ind. short wave to spine.
(L)	78	80	88	200	83	280	90	1800			
(R)	105	100	115	150	90	150	143	210	Intermittent claudication for 6 mo.	Atrophy of skin and nails. Marked rubor at heart level. Impending gangrene, L. ft.	Ind. short wave to spine. Intermit. venous occlusion.
(L)	110	120	120	200	95	500	140	2400+			
(R)	90	80	140	175	160	300	165	435	Intermittent claudication in left calf for 3 mo. Nocturnal pain.	Atrophy of skin and nails.	Ind. short wave to spine. Intermit. venous occlusion.
(L)	110	115	160	250	150	1110	170	2400			
(R)	95	200	120	180+	140	1800	240	3000	Amputation of 2nd toe of left ft. 6 yr. before. Pain in rt. ft. for 4 mo.	Marked atrophy of skin and nails. Rose spots on both ft. Rt. big toe, red and swollen.	Referred to surgery.
(L)	85	140	95	175	135	190	140	900+			
(R)	48	35	53	40	60	240	43	360	Gangrene of toes of both ft. following radiant heat to ft. 2 wk. before.	Gangrene of toes. Atrophy of skin and nails.	Intermit. venous occlusion.
(L)	48	30	58	100	58	150	58	1800			
(R)	90	145	110	1800	140	5400+	150	3600	Infection and amputation of 4 toes on left ft. during preceding 10 yr.	Infected fissure between 3rd and 4th metatarsals on left ft. Small ulcers of skin.	Ind. short wave to spine. Conservative treatment.
(L)	125	200	150	900	125	2400+	170	2400+			
(R)	75	50	75	70	110	360	80	5400	Intermittent claudication for years. Redness and swelling of rt. ft. for 6 wk.	Gangrene of rt. ft.	Referred to surgery.
(L)	55	40	60	180	70	480	90	3600			

TABLE

PATIENTS FOLLOWED OVER A PERIOD OF TIME, ILLUSTRATING THE VALUE

SUBJECT AND DIAGNOSIS	AGE	OSCILLOMETRIC READINGS			HISTAMINE TEST*	SKIN TEMPERATURE
		THIGH	LEG	FOOT		
<i>Females</i>	49					
H. M. (R.H.D. + A.F. + Embolus to left femoral artery.)		(R) 3	2	$\frac{1}{4}$		(R) Skin temp. of big toe = 33.0° C. (L) Skin temp. of big toe = 28.7° C.
		(L) $\frac{1}{2}$	0	0		
		(R) 2	3 $\frac{1}{4}$	0		(R) No change in big toe—27.1° C. to 26.6° C. (L) Increase in big toe from 29.3° C. to 30.4° C.
		(L) $\frac{1}{8}$	0	0		
		(R) 2 $\frac{1}{2}$	4 $\frac{1}{4}$	$\frac{1}{4}$	(R) Sl. delay in ft., ank. and thigh; good in leg. (L) Marked delay in ank.; sl. delay in ft. and thigh; good in leg.	(R) Skin temp. of big toe = 29.5° C. (L) Skin temp. of big toe = 30.2° C.
		(L) $\frac{1}{2}$	$\frac{1}{4}$	0		
		(R) 4	5	$\frac{1}{4}$		
		(L) $\frac{1}{2}$	$\frac{1}{4}$	S.P.		
L. D. (D.M. + Arterio- sclerosis obliterans)	52	(R) 1 $\frac{1}{2}$	$\frac{1}{4}$	0	(R) Sl. delay in ank., leg and thigh; good in ft. (L) Mod. delay in ft. and ank., good in leg and thigh.	(R) Skin temp. of big toe = 28.6° C. (L) Skin temp. of big toe = 28.1° C.
		(L) $\frac{1}{8}$	$\frac{1}{4}$	0		

*See text for explanation of notations of the histamine test.

†Th. = Threshold in seconds.

‡C. T. = Clearing time in seconds.

D. M. = Diabetes mellitus.

A. F. = Auricular fibrillation.

R. H.D. = Rheumatic heart disease.

III

OF THE REACTIVE HYPEREMIA RING TEST IN EVALUATION OF THERAPY.

REACTIVE HYPEREMIA RING TEST								PERIOD OF SYMPTOMS	LESION	THERAPY
THIGH		LEG		ANKLE		FOOT				
TH.†	C.T.†	TH.	C.T.	TH.	C.T.	TH.	C.T.			
(R) 35	90	35	130	35	120	30	180	Tingling and burning sensations in soles of feet.	Sl. pallor of left ft. as compared to rt.	None.
(L) 53	90	40	75	20	140	40	90			
(R)		35	200	35	200	54	390	Extreme pain and coldness of left leg and ft. for 12 hr.	Pallor of left leg and ft. Dusky cyanosis of toes.	Ind. short wave to spine. Oscillating bed. Papaverine.
(L)		60	255	45	255	58	1200+			
(R) 43	65	43	93	43	100	45	105	(3 mo. on oscillating bed) (1 mo. after cessation of oscillating bed therapy.) (Complete recovery)		
(L) 68	60	58	80	48	200	58	275			
(R) 38	30	48	65	50	60	53	85	Ulcer of left ft. for 1 yr. Nocturnal pain.	(R) Sl. atrophy of skin and nails. (L) Healed ulcer over ext. malleolus. Ft. swollen and erythematous over dorsum.	Ind. short wave to spine.
(L) 58	30	58	48	68	55	58	240			
(R) 73	65	73	100	73	160	85	150	(Put on oscillating bed)		
(L) 58	45	68	140	90	225	80	340			
(R) 73	60	73	120	75	175	100	440	(3 wk. on oscillating bed) (Great clinical improvement) (Nails starting to grow again) (6 wk. on oscillating bed) (Thermostatic heat cradle applied) (Exacerbation of symptoms) (10 wk. on oscillating bed)		
(L) 65	60	70	130	85	380	160	3600+			
(R) 75	70	75	250	90	320	105	1200			
(L) 85	100	90	255	115	1200	110	3600+			
(R) 68	70	68	170	65	330	80	245			
(L) 75	110	85	250	98	720	180	1200			
(R) 90	80	85	85	90	450	110	900			
(L) 80	85	85	110	98	300	270	3600+			

indicated by Montgomery, et al.,⁴ no great amount of information is therefore derived from such studies in clear-cut cases of organic obliterative disease of the arteries, except as collateral evidence.

One interesting observation, not generally made, was that the skin temperature in the most affected extremity was frequently higher than that of the least affected extremity; this occurred in the absence of demonstrable inflammatory lesions. It is evident that some natural mechanism exists whereby the remaining vascular channels open up once the blood supply to an extremity has reached a certain degree of obliteration and after the obliteration has persisted for a period of time. Again, oscillometric readings and reflex dilation tests do not ordinarily reveal this improvement in the local circulation. The need of a means of accurately ascertaining the functional capacity of the finer circulation is thus strikingly brought forth. Indeed, as will be demonstrated later, *the lesions and symptomatology are far more exactly related to the functional capacity of the finest vessels than to that of the larger arterial trunks.* Evidence has also been previously presented² that there is an expected and natural ageing of these fine vessels which is entirely independent of arteriosclerosis of the larger vessels. Furthermore, the influence of pronounced seasonal changes on the responsiveness of these fine vessels in relation to outside temperature must not be overlooked.*

The Histamine Test versus the Reactive Hyperemia Ring Test.—The histamine test, as indicated above, was done to corroborate the results of the segmental R.H.R.T.† When the histamine injection caused a wheal to appear at a particular site within two and one-half minutes, the response was regarded as normal; when the wheal appeared within five minutes it was regarded as slightly delayed, and, in ten minutes, as moderately delayed; failure to appear within ten minutes constituted a greatly delayed reaction. No attempt was made to appraise the appearance and disappearance of the local red reaction and arteriolar flare in these tests because they were found to be too variable.

As shown in Table I, there was a fair correlation between the degree of delay in the histamine responses and the extent of symptoms and lesions. However, there were many cases of marked discrepancy. In Case F. D., in the male group, the patient had only moderate delay in the ankle and slight delay in wheal formation in his left foot, but he had one of the most severe lesions of the group, namely, gangrene of the fourth and fifth toes. On the other hand, in Case M. L., also in the

*It is unfortunate that during the course of this investigation it was not possible to make accurate observations on the incidence of arteriosclerotic vascular lesions in relation to the seasons. It is the authors' casual observation, however, that the number of admissions and the morbidity of arteriosclerotic vascular lesions are greatly increased in midwinter on the various services of Kings County Hospital. Since such a seasonal variation in the number of admissions might arise from other causes, no sound conclusion may be drawn. An extended study of the effects of season on peripheral vascular disease is desirable.

†Hereafter, the reactive hyperemia ring test will be indicated by the abbreviation R. H. R. T.

male group, there were markedly delayed histamine reactions on the right foot, but only slight atrophy of the skin and nails of this foot was found on examination.

Since the clearing time of the R.H.R.T. has been shown to be related to the rate of blood flow in the skin,^{1, 2} and the length of time required for the histamine wheal to appear is also said to be related to cutaneous blood flow,^{3, 4, 5} a comparison of the relative worth of these two tests can be made. Considering these tests only in the foot and ankle, it may be seen from Table I that most histamine wheals which were interpreted as normal corresponded to a clearing time of less than 300 seconds. Those which were slightly or moderately delayed fell in a group of clearing times of less than 500 seconds, although some corresponded to clearing times of 1,000 or more seconds. A marked delay in the appearance of the histamine wheal in a few cases accorded with a clearing time of over 2,000 seconds. Paradoxically, in some patients a greatly delayed histamine wheal was obtained with clearing times of less than 250 seconds, and in the presence of a clinically good skin circulation, with absence of marked symptoms and lesions. The converse also was not infrequently noted (Table I).

To what causes these apparent deficiencies in the histamine wheal test may be ascribed cannot be immediately ascertained. A closer survey of the exact relationship of the segmental thresholds of reactive hyperemia in the skin of the lower extremities and the extent of vascular obliteration and symptomatology may now be undertaken, not only to explain this paradox, but also to ascertain whether, in the quantitation of these thresholds, a better means of evaluating the functional loss of the cutaneous circulation is not readily available.

The Relationship of the Type of the Lesion and the Results of the Reactive Hyperemia Ring Test.—These results must be considered against a background of the natural segmental and ageing characteristics of the skin of the lower extremities.* Since most of our subjects were in the fifth and sixth decades, the normal for these patients may be briefly stated. There is a gradual rise in the *threshold* of reactive hyperemia caused by local ischemia which rises from about 50 to 75 seconds in the upper part of the thigh to about 90 to 200 seconds in the dorsum of the foot, and the corresponding *clearing times* rise from about 60 to 90 seconds in the thigh to 100 to 300 seconds in the foot. In a few isolated cases, the clearing time normally may be as high as 600 seconds in the skin of the ankle and foot.

Invariably, in all the cases of arteriosclerosis obliterans which we studied, the segmental thresholds of reactive hyperemia in the lower extremities were in no way significantly different from the expected normal. This held true for the patients with minimal symptoms and signs, as well as for those with far-advanced lesions, such as gangrene of the toes.

*For a complete account of this subject, see preceding article in this issue.

Indeed, in some instances the threshold was considerably lower on the affected side. Case M. F., Table I, is a good example of this.

It is well known that dilation of small vessels occurs even when the circulation is completely occluded in acute experiments,¹² and it has further been shown that the threshold of reactive hyperemia caused by local ischemia in the skin is not altered under these conditions.^{1, 2} What occurs when various grades of occlusion are maintained over periods of weeks or months has not been studied. Since these patients with obliterative vascular disorders really constitute a naturally conducted experiment along these lines, the results of this study actually supply the answer to this problem.

It is at once distressing and gratifying to know that there is no diminution in the capacity of these fine skin vessels to respond by reactive hyperemia to local ischemia in cases of long-standing obliteration of the vascular tree. It is disturbing, for it indicates that therapy which aims to improve the capacity of these fine vessels, such as mechohyl iontophoresis, local heat, intermittent venous occlusion, etc., are superfluous unless, of course, they also appreciably improve the blood supply to these fine vessels, especially in instances of advanced obliteration of larger arterial trunks. That these therapeutic agents are capable of achieving this in peripheral vascular disorders has not yet been thoroughly proved.^{13, 14, 16, 17} On the other hand, it is pleasing to learn that, even with extreme degrees of obliterative disease, continuing over a period of years, the ability of these fine vessels to respond by hyperemia to local ischemia is in no way impaired. *This indicates that therapeutic procedures must aim largely at improving local blood flow, and need not induce hyperemia.* Perhaps this explains the success of such methods as Buerger's exercises and the oscillating bed, which passively increase local blood flow without causing dilation of vessels. Vice versa, the failure of the intermittent venous occlusion devices and the suction boot, which primarily produce intense hyperemia as a means of increasing blood flow, is explicable in the same way.*

When the clearing times of the R.H.R.T. were compared with the symptoms and extent of the lesions, an excellent correlation was found. The patients were grouped as indicated in Fig. 1. Many patients who were referred to us with a diagnosis of peripheral vascular disease had no discernible lesions of their extremities. However, on performing a modified plantar ischemia test,⁷ slight pallor was noted with elevation, and some rubor with dependency, of the feet. This group of patients, along with perfectly normal ones, were placed in Group I, whereas Group II, in addition, had some atrophy of the skin and nails. To Group III were assigned those patients who, besides presenting the lesions above mentioned, also suffered from nocturnal pain and claudica-

*The authors' viewpoints concerning the efficacy of these therapeutic devices is based not only upon their own clinical experience, but also on that of others.^{13, 14, 16, 17}

tion of such degree that they were not able to walk farther than two city blocks at a moderate pace before they were forced to stop and rest. Those who presented the well-known syndrome of impending gangrene were put in Group IV, and those with actual gangrene, in Group V.

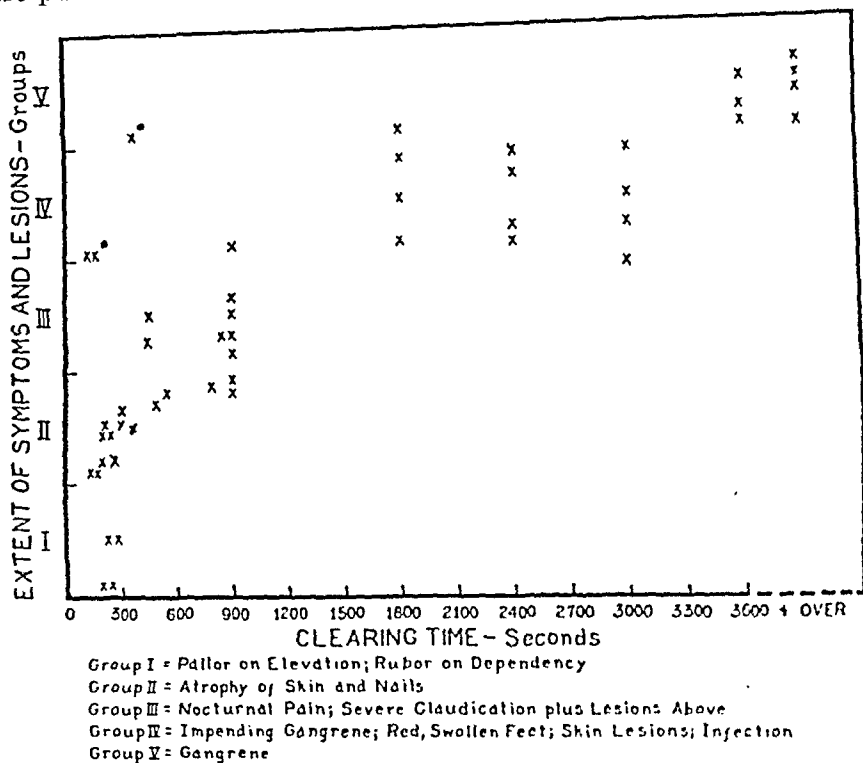


Fig. 1.—The clearing times of the reactive hyperemia ring test in the ankle and foot are plotted against the severity of symptoms and extent of lesions, as grouped above. Patients marked by asterisks had received treatment which made their lesions worse (see text for discussion).

As is shown in Fig. 1, the clearing time of the R.H.R.T. was longer in proportion to increasing severity of the lesions. Thus, all patients in Group I had a clearing time of less than 300 seconds; those in Group II, one of 200 to 600 seconds; those in Group III, one of 400 to 900 seconds; and those in Group IV, one of 1,000 to 3,000; those in Group V generally had one of 3,000 seconds or over. It is interesting that two patients who fell outside the general mean (marked by asterisks in Fig. 1) had received a form of treatment which caused a lesion more advanced than the degree of their obliterative process would indicate that they should have had. These were S. S., of the females (Table I), who had an ingrown toe nail removed, and M. S., of the males (Table I), who acquired gangrene of his toes after the application of radiant heat to his feet.

Since the clearing time has been repeatedly shown by various means to be directly related to blood flow in the smallest vessels of the skin,^{1,2} the implication of these results is obvious. The skin lesions which any patient will incur in the course of his vascular disease is a result, not

TABLE II
CASES OF EMBOLISM, ILLUSTRATING THE VALUE OF THE REACTIVE HYPEREMIA RING TEST IN INDICATING THE FORM OF THERAPY AND THE PROGNOSIS

SUBJECT AND DIAGNOSIS	AGE	OSCILLOMETRIC READINGS				HISTAMINE TEST*	SKIN TEMPERATURE	REACTIVE HYPEREMIA RING TEST										PERIOD OF SYMPTOMS	LESION	THERAPY
		THIGH		LEG				THIGH		LEG		ANKLE		FOOT						
		TH.†	C.T.†	TH.†	C.T.†			TH.†	C.T.†	TH.†	C.T.†	TH.†	C.T.†	TH.†	C.T.†					
<i>Females</i> L. L. (D.M.) + A.S.H.D. + A.F. + Embolus to left femoral artery)	68	(R) 1‡	2‡	‡		(R) Good in all parts. (L) Marked delay at all points below knee.	(Not done)	(R) 53 (L) 60	40 35	55 65	60 190	55 75	118 400	85 120	255 3600+	Intense pain and coldness of left leg and ft. for 24 hr.	Pulseless, cold left ft. Dusky cyanotic toes.	Pavac boot. Papaverine.		
A. H. (R.H.D.) + A.F. + Embolus to left femoral artery)	42	(R) 5 (L) 0	5 0	‡ 0		(R) Good in all parts. (L) Marked delay at all points below mid thigh. Complete absence of wheel below knee.	(R) Skin temp. of big toe = 29.0° C. (L) Skin temp. of big toe = 24.0° C.	(R) 75 (L) 150	60 120	75 240	220 1800	70 (Complete absence of hyperemia after stimulation for 10 min.)	720	90	480	Intense pain, coldness and pallor of entire left leg for 8 hr.	Pulseless, cold left leg.	Referred to surgery.		

*For explanation of notations of the histamine test see text.

†Th. = Threshold in seconds.

‡C. T. = Clearing time in seconds.

D. M. = Diabetes mellitus.

A. F. = Auricular fibrillation.

R. H. D. = Rheumatic heart disease.

A. S. H. D. = Arteriosclerotic heart disease.

of a diminution in the ability of these fine vessels to respond to injury by reactive hyperemia, but simply of the degree of slowing of blood flow within them.

The Reactive Hyperemia Ring Test in Cases of Embolism.—Segmental quantitation of the threshold and clearing times of reactive hyperemia in the skin of an extremity with an embolus in its major artery was found to be not only an excellent aid in indicating the form of therapy to be used, but also a prognostic method. Two illustrative cases are listed in Table II. Both patients were referred to us with a diagnosis of embolism of the femoral artery. In case L. L. (Table II) the patient was found, clinically and oscillometrically, to have all the signs of this condition. However, the R.H.R.T. showed readings which were not far from normal down to the ankle, and, in the foot, no worse than had been observed in many cases of long-standing arteriosclerosis obliterans. Consequently, conservative therapy was instituted, with satisfactory results.

On the other hand, in case A. H. the patient presented a much more serious clinical picture and the question of performing embolectomy arose. Because the R.H.R.T. showed a remarkable rise of threshold and clearing time, even in the thigh, and complete absence of any response in the leg and foot, even after application of local ischemia for a period as long as 10 minutes, it was felt that a surgical procedure was indicated, and that the limb could not be saved by conservative measures. Unfortunately, the patient died of cerebral embolism before she could be operated upon.

In the interest of brevity, no other similar cases will be described, but it is clear that when it is impossible to obtain a hyperemia response after application of the weighted ring to the skin for a reasonable period of time (10 minutes), not only is there complete cessation of blood flow in these fine vessels, but, also, irreparable damage has probably taken place. This statement is made because, in acute experiments, in which complete stagnation of blood flow is produced by a tourniquet, the hyperemia response is easily obtained,^{1, 2} and it is only the clearing time which is markedly altered. In addition, even with systemic anoxemia of only 30 minutes' duration, there is a very marked decrease in the sensitivity of these fine vessels,¹⁵ indicating that prolonged oxygen lack may cause extensive damage.

When, however, with embolism of a major artery, the segmental thresholds and clearing times do not differ significantly from those in cases of the most severe arteriosclerosis obliterans (see Table I), it is reasonable to assume that the limb can be saved by conservative measures. One such case is H. M., in Table III.

Evaluation of Therapy by Means of the Reactive Hyperemia Ring Test.—We were fortunate in that we did this test on patient H. M., Table III, before complete embolism of the left femoral artery had taken place. She was referred to us because she complained of tingling

and burning sensations in the soles of her feet. Despite the presence of auricular fibrillation, and because her skin circulation was so nearly normal, it was felt that the diagnosis of embolism was questionable, and that she might instead be suffering from an obliterative vascular disorder. Twelve hours later, however, she experienced sudden, sharp, severe pain in her left foot. At this time the R.H.R.T. showed a remarkable change. Clearing times were more than doubled in the affected leg, and, in the foot, rose to over twenty minutes. Noteworthy, too, is the fact that the oscillometer readings did not change significantly. She was treated with an oscillating bed and indirect short wave diathermy to the lower part of the spine. Three months later the clearing times had returned to almost normal levels, and one month later, after cessation of hospital treatment, she showed even further improvement, with complete symptomatic recovery (Table III).

Another patient (L. D., Table III) is illustrative of the conservatism needed in the treatment of advanced obliterative vascular disease. Early in the fall her R.H.R.T. showed slight impairment of the skin circulation. She was given conservative treatment, but, because of her lack of cooperation, her lesion became worse, and she was forced to enter the hospital in December.* The clearing time of the R.H.R.T. in the foot rose to more than one hour at this time. She was put on an oscillating bed. At the end of three weeks the R.H.R.T. showed an even greater slowing of skin circulation, but at the end of six weeks there had been considerable improvement, as measured by this test (Table III). The clinical picture also was changed for the better. The nails had started to grow afresh, and the nocturnal pain was much diminished. At this time it was thought that a thermostatic heat cradle, applied to the feet, would speed recovery. The thermostatic mechanism failed to work, however, which permitted the environmental temperature about the feet to rise to excessive levels. There was again an exacerbation of symptoms, and the R.H.R.T. showed slowing of skin circulation almost to pre-therapy levels.

In the above cases, therefore, the R.H.R.T. was the only criterion upon which reliance could be placed in following the course of therapy. It is well known that oscillometric readings are rarely improved by therapy. Thermometry is more useful for vasodilation tests and in vasospastic disorders than in arteriosclerosis obliterans. The histamine test is not quantitative enough to be an accurate guide of the efficacy of therapy. Plethysmographic studies are beyond the scope of ordinary clinical facilities. A simple, reliable bedside test which is capable of indicating the local blood flow in the skin is the clearing time of the R.H.R.T. This should prove to be valuable because it is the circulation in these finest vessels upon which ultimately rests the maintenance of the

*This case illustrates the authors' observation that seasonal changes may alter the course of a peripheral vascular lesion. It may well be that the advent of cold weather exerted an adverse influence upon this patient's lesions.

functions of the skin, and for which therapeutic procedures are instituted, and it is these which determine resistance against infections and pregangrenous changes.

SUMMARY AND CONCLUSIONS

Twenty-four cases of typical arteriosclerosis obliterans were carefully studied by the usual oscillometric and thermometric methods and histamine wheal tests, and also by ascertaining the segmental thresholds of reactive hyperemia in the lower extremities, using a method recently developed. The relationships of these tests to each other and to the natural gradient and ageing variations of reactive hyperemia in the human skin are described. The inadequacies of the several existing tests are pointed out. A simple reactive hyperemia ring test has been shown to be a reliable means of evaluating the skin circulation of the lower extremities in arteriosclerosis obliterans.

Two cases of embolism of the femoral artery and two patients who received a particular form of therapy and were followed over a long period of time are described to further demonstrate the implications and value of the reactive hyperemia ring test in these conditions.

The following conclusions were reached:

1. There is no exact correlation between slowing of the skin circulation and oscillometric readings.
2. There is, in general, fair agreement between the delay in histamine wheal formation and the clearing time of the reactive hyperemia ring test.
3. The thresholds of the reactive hyperemia ring tests in the ankle and foot are the same as the expected normal for the age group involved. This means that there is no decrease in the capacity of the smallest blood vessels of the skin to respond by reactive hyperemia to local ischemia, even in advanced stages of obliteration of arterial trunks.
4. The clearing times of the reactive hyperemia ring tests are directly proportional to the severity of symptoms and extent of lesions in the ankle and foot. Although the normal clearing time in the foot is under 300 seconds, it may rise to over 3,600 seconds in a foot with gangrenous changes.
5. The loss of function of the fine skin vessels, which renders the skin susceptible to infection and gangrene in the ankle and foot, is not caused by inability of these vessels to respond by reactive hyperemia, but merely by a profound slowing of blood flow within them.
6. In cases of complete embolic obstruction of the major arteries of the lower extremities, the small skin vessels may completely lose the ability to respond to local ischemia by reactive hyperemia. On the other hand, with partial embolic obstruction, or with good collateral blood flow, the hyperemia responses are comparable to those in cases of advanced arteriosclerosis obliterans.

7. The reactive hyperemia ring test offers a simple, exact, objective method of evaluating the effect of therapy, over a long period of time, upon the skin circulation of the lower extremities.

We wish to express our sincere gratitude to Dr. S. R. M. Reynolds, now at the Carnegie Institution of Washington. His unfailing inspiration and material aid have made this work possible.

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CARDIOVASCULAR EFFECTS OF DESOXYCORTICOSTERONE ACETATE IN MAN

W. RAAB, M.D.
BURLINGTON, VERMONT

THE fundamental importance of adrenal cortical hormones in muscular metabolism and activity is obvious from the typical muscular adynamia in Addison's disease and after experimental adrenalectomy, and from its abolition through treatment with cortical extracts. Similar phenomena apply to the vascular tone of the blood vessels as manifested in the blood pressure level.

Indications of myocardial weakness after adrenalectomy and in Addison's diseases were recorded by several investigators,¹⁻⁴ and the heart was found to be markedly reduced in size in these conditions.^{3, 5-7}

On the other hand, there is also evidence that an excess of cortical hormonal substances is likely to interfere with normal heart action and size, as demonstrated by:

(a) the occurrence of congestive heart failure in patients with adrenal cortical tumors;⁸

(b) the appearance of marked cardiac dilatation with dyspnea, pulmonary and peripheral edema in Addison patients treated with an overdosage of cortical extracts or desoxycorticosterone acetate;⁹⁻¹⁶

(c) the appearance in the heart muscle of the rat of abnormally large amounts of adrenalin-like substances after injections of desoxycorticosterone acetate;⁷

(d) the presence of an abnormal amount of adrenalin in the enlarged and dilated heart muscle of a patient with tumors of the cortex who had died from congestive heart failure.¹⁷

(e) the production of changes of the electrocardiogram (T waves) of dogs through the administration of desoxycorticosterone acetate.¹⁸

Furthermore the suprarenal cortical hormones appear to participate in the maintenance of pathologically high blood pressure levels. Experimental renal hypertension is partly dependent upon the presence of cortical hormonal material;^{19, 20, 21} abnormal elevation of the blood pressure following the administration of cortical sterols has been observed in animals^{22, 23} and in patients with^{12, 16, 24} or without Addison's disease.²⁵ Hyperplasia and adenomas of the suprarenal cortex are common features in persons with essential hypertension.^{8, 26, 27}

From the University of Vermont, College of Medicine, Department of Medicine, Burlington.

This study was aided by a grant from the Rockefeller Foundation.

Received for publication Dec. 17, 1941.

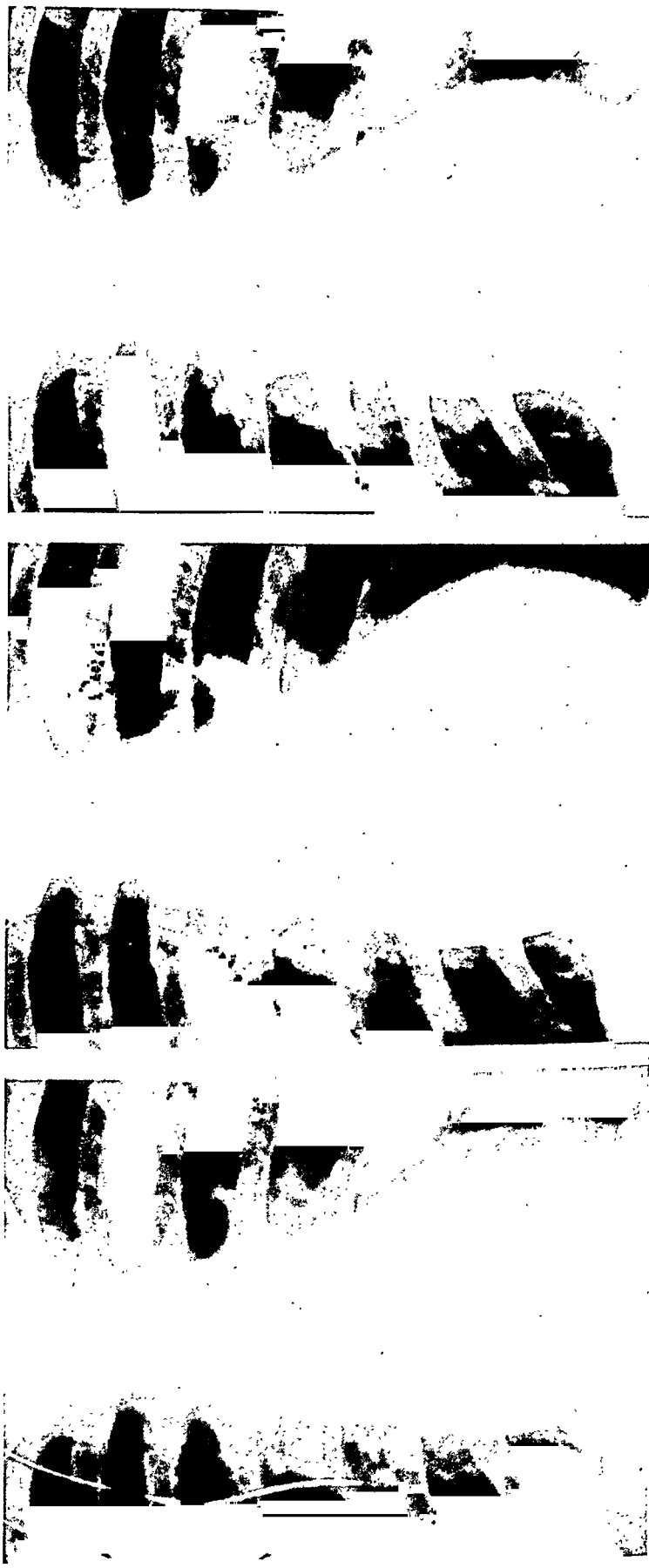


Fig. 1.—Case 3. The heart before treatment, immediately following five daily injections of desoxycorticosterone acetate (20 mg. each) and one week later.

The above-mentioned facts are suggestive of a pathogenic role of cortical sterols in the pathogenesis of arterial hypertension and of myocardial damage and failure. It appeared interesting, therefore, to study the effect of such substances upon the normal human heart and vascular system.

Desoxycorticosterone acetate was used for this purpose since it is the most readily available of the various physiologically active cortical sterols although it is known that other cortical fractions exert a more marked influence, at least upon the skeletal muscle.²⁸

Apart from a few experiments in which "Cortate"* was used, most experiments were carried out with "Doca."†

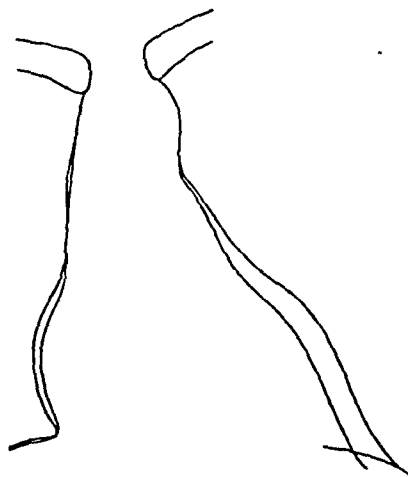


Fig. 2.—Case 8. The heart before treatment (inner contour) and immediately following three daily injections of desoxycorticosterone acetate (50 mg. each) (outer contour).

PROCEDURE

Eleven healthy male students and one patient with bronchial asthma were treated for varying numbers of days (three to fourteen) with daily intramuscular doses of 20 to 50 mg., totaling 100 to 330 mg. of desoxycorticosterone acetate (d. c. a.).

The following features were recorded before and during the treatment and twenty-four hours after the last injection: blood pressure, pulse rate, roentgenogram of the heart, electrocardiogram, body weight, concentration of adrenalin and adrenalin-like compounds in the blood and their "specific ratio,"²¹ effect of adrenalin injection and of physical²⁹ exercise upon blood pressure, pulse rate and electrocardiogram.

BLOOD PRESSURE

There were no characteristic changes except a moderate rise of the systolic pressure in two cases (Cases 4 and 10) at the time of the conclusion of the experiments.

*Schering.

†A very generous supply had been received from the Roche Organon, Inc.

PULSE RATE

In eight cases there were no characteristic changes. In three of the healthy students there was a temporary tachycardia: in Case 4 108 vs. 84 beats; in Case 10 110 vs. 75 beats, only on the second and third days; in Case 9 112 vs. 84 beats, only on the second day.

In Case 12 (a patient with bronchial asthma) a marked bradycardia prevailed for the duration of the experiment. The pulse rate decreased steadily from 80 to 48 beats per minute.

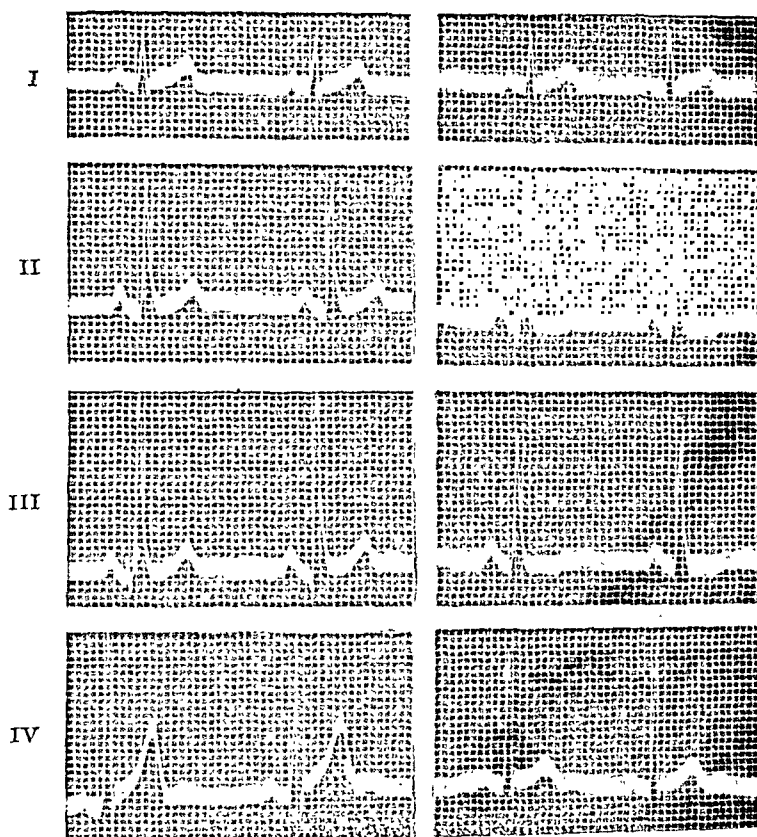


Fig. 3.—Case 8. Electrocardiogram before and four weeks after desoxycorticosterone acetate injection.

DIAMETER OF THE HEART

In making radiograms of the heart before and after the treatment with d. c. a. care was taken to duplicate the position of the diaphragm as accurately as possible in order to obtain comparable results.

In nine of the twelve cases there were enlargements of the diameter of the heart shadow ranging from +4 to +17 mm. with an average of +6 mm. These enlargements concerned only the ventricles and disappeared again within about a week after discontinuation of the drug (Figs. 1 and 2).

ELECTROCARDIOGRAM

The electrocardiograms taken after the d. c. a. treatment as compared with the controls taken before the d. c. a. injections showed distinct

alterations of the "anoxic" type in those two students (Cases 8 and 9) who had received the highest single doses (50 mg. per day), namely, lowering or inversion of the T waves and depression of the S-T segments which persisted from a few days to as much as 4 weeks (Figs. 3 and 4).

A survey of the electrocardiograms of all of the eleven healthy students showed that lowering of the T waves was the only feature commonly observed (Table II). It was present in the first lead in six cases, in the second lead in eight cases, in the third lead in nine cases, in the fourth lead in seven cases.

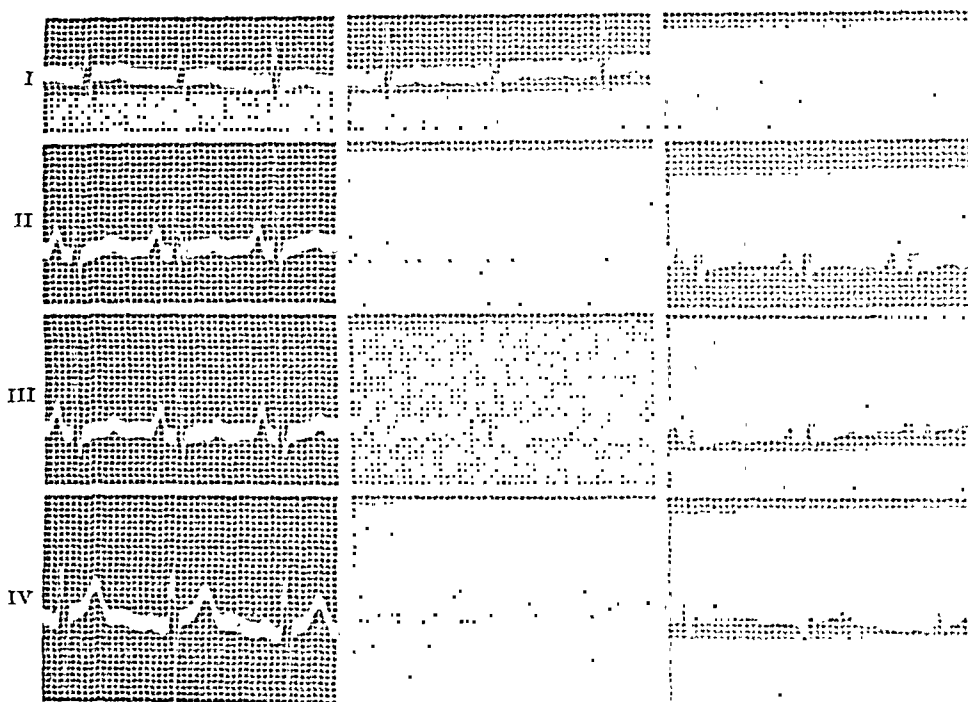


Fig. 4.—Case 9. Electrocardiogram at rest before desoxycorticosterone acetate, twenty-four hours after last desoxycorticosterone acetate injection, and again one week later.

In Case 7 the P wave was almost completely absent in Leads II and III (Fig. 5) after the d. c. a. injections.

The R wave was somewhat lowered in the third lead in five cases.

In Case 12, a 37-year-old patient with bronchial asthma, emphysema, a small heart and some cyanosis, the electrocardiogram was abnormal from the beginning. The injections were followed by marked bradycardia and changes of the P and T waves in the three first leads and of the QRS complex in the first lead (Fig. 6).

BODY WEIGHT

There was an increase in weight in all instances beginning with the day of the first injection and ranging from 1.25 to 6.5 lb. The maxima were reached between the second and eighth days of treatment.

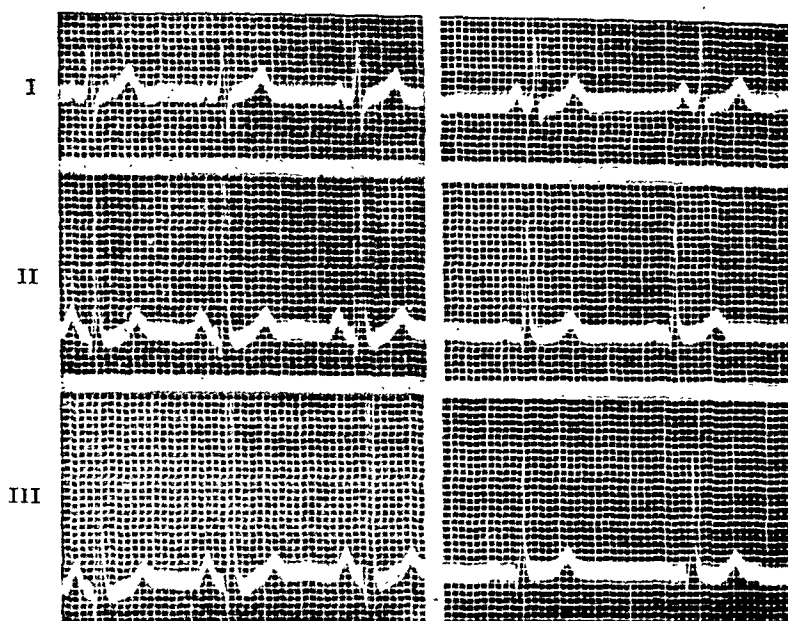


Fig. 5.—Case 7. Electrocardiogram at rest before and twenty-four hours after desoxycorticosterone acetate injections.

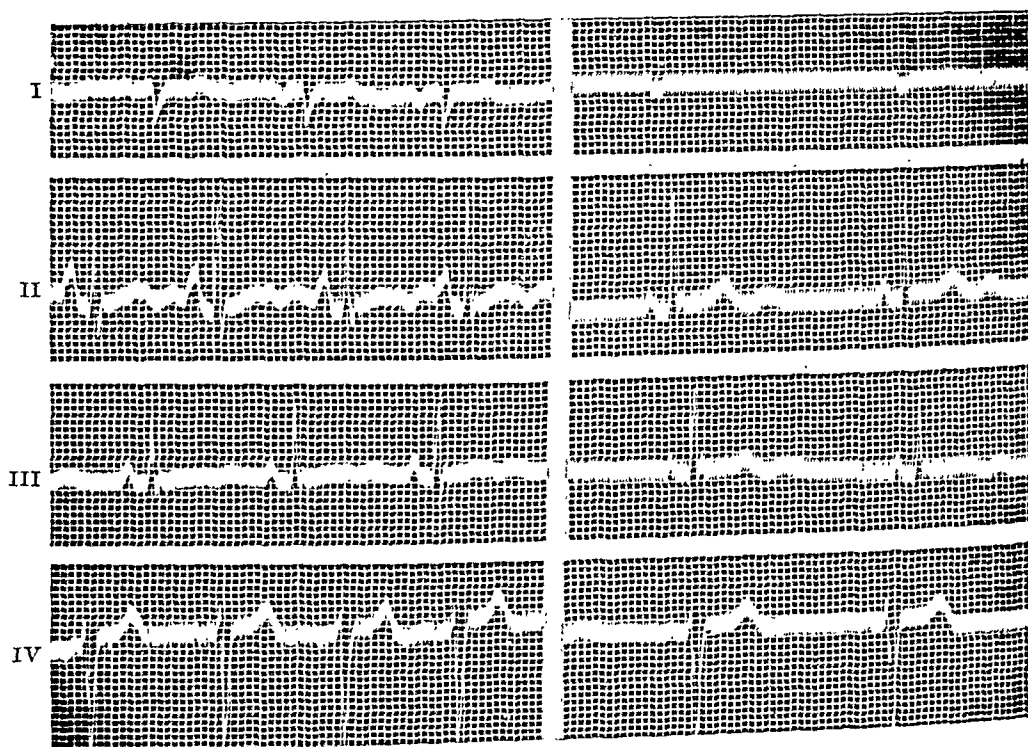


Fig. 6.—Case 12 (bronchial asthma). Electrocardiogram at rest before and twenty-four hours after desoxycorticosterone acetate injections.

LEVEL OF ADRENAL HORMONES IN THE BLOOD

The determinations were done before the first and twenty-four hours after the last injection. The colorimetric findings obtained with the modified method of Shaw²⁹ were originally believed to be composed of both adrenalin and of cortical sterols bound to it.^{7, 29, 30} However, recent investigations which were carried out upon the suggestion of Dr. E. C. Kendall make the direct participation of sterols doubtful and make it appear more likely that the results are due chiefly to adrenalin plus certain adrenalin-like compounds (sympathin? adrenalone?).

EFFECT OF ADRENALIN ON SYSTOLIC BL. PR. INCREASED THROUGH PRETREATMENT WITH DESOXYCORTICOSTERONE ACETATE

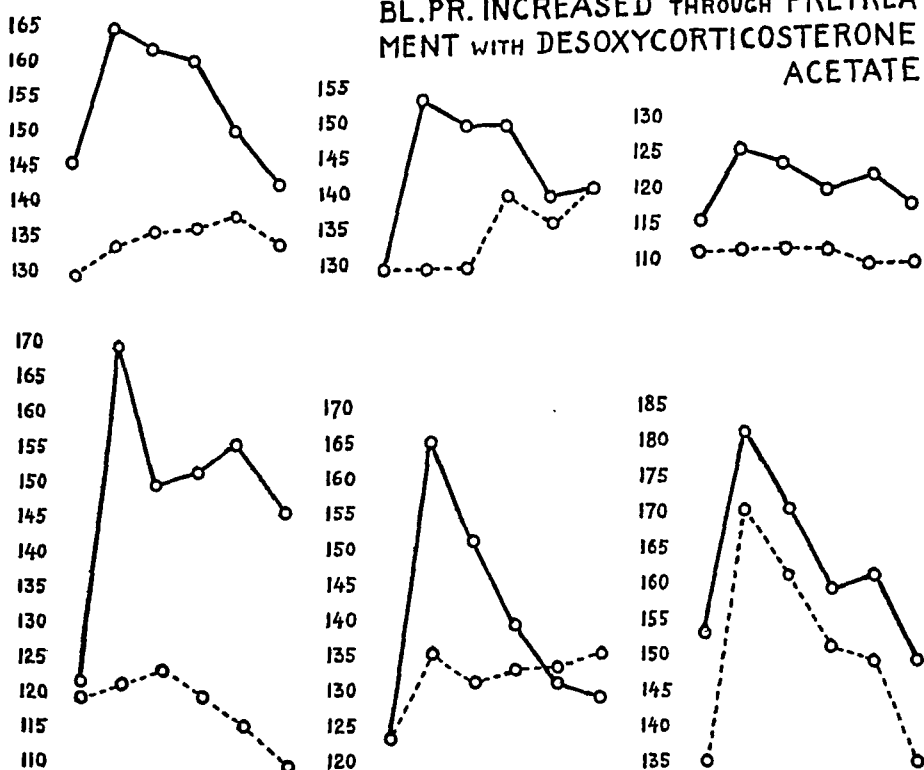


Fig. 7.—The blood pressure readings were taken at intervals of six minutes, before and following the subcutaneous injection of 0.4 to 0.5 mg. of adrenalin. Dotted lines, before treatment with d.c.a.; solid lines, after treatment with d.c.a.

While the behavior of the total colorimetric values was found to be uncharacteristic after injections of d. c. a., there was in all but two instances a fall of the "specific ratio," indicating a higher proportion of adrenalin proper taking part in the total colorimetric findings.

ALTERED EFFECT OF ADRENALIN INJECTION

The effect of subcutaneously injected adrenalin (0.4 to 0.5 mg.) upon the systolic blood pressure was markedly increased in all six persons pretreated with d. c. a. (Fig. 7), while the reactions of the diastolic pressure and of the pulse rate remained practically unchanged.

TABLE I

CASE NO.	AGE (YEARS)	TOTAL DOSE (MG.)	GIVEN IN DAYS	BLOOD PRESSURE		PULSE RATE		CHANGE IN HEART DIAMETER (MM.)	INCREASE IN BODY WEIGHT (LB.)	ADRENAL HORMONES IN BLOOD (COLOR UNITS)		SPECIFIC RATIO OF ADRENAL HORMONES	
				BEFORE D.C.A.	AFTER D.C.A.	BEFORE D.C.A.	AFTER D.C.A.			BEFORE D.C.A.	AFTER D.C.A.	BEFORE D.C.A.	AFTER D.C.A.
1	23	100	5	124/60	124/66	78	80	+ 9	2.5	169	100	1:1.20	1:1.43
2	25	100	5	120/60	116/60	70	64	0	4	152	194	1:1.06	1:1.41
3	25	100	5	114/70	116/70	72	62	+17	3	139	193	1:1.00	1:1.43
4	24	110	4	136/84	154/84	84	108	- 3	1.5	70	139	1:1.29	1:1.74
5	26	120	4	130/88	130/80	76	82	+ 5	5	50	77	1:0.81	1:1.54
6	22	150	5	112/70	116/72	94	84	- 3	3	169	169	1:1.13	1:1.49
7	25	150	5	112/66	120/78	84	78	+ 5	1.25	159	62	1:1.27	1:1.82
8	26	150	3	116/74	116/70	72	72	+14	1	112	110	1:1.60	1:1.32
9	31	150	3	148/96	146/102	84	96	+ 9	1.5	60	57	1:1.20	1:1.32
10	23	160	4	122/72	142/60	75	72	+11	5.5	103	156	1:0.76	1:1.11
11	24	330	14	122/72	117/67	74	80	+ 7	6.5	146	102	1:1.32	1:1.27
12*	37	120	6	130/80	146/90	80	48	+ 4	3	286*	240	1:1.27	1:1.41
Av.	26	150	5	124/74	129/74	78	76	+ 6	3.2	135	183	1:1.16	1:1.44

*Bronchial asthma, abnormally high blood level of adrenal hormones, abnormal electrocardiogram.

In all instances there was a slight lowering of the T waves in at least two leads of the adrenalin electrocardiograms (taken twelve minutes after the injection) after pretreatment with d. c. a. compared with those which had been taken after adrenalin injection without d. c. a. pretreatment (Table II).

TABLE II

AVERAGE CHANGE IN THE HEIGHT OF THE T WAVES AFTER TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	D.C.A.* ALONE (MM.)	ADRENALIN† S.C. (MM.)	PHYSICAL EXERCISE‡ (MM.)
Lead I	-0.1	-0.15	-0.3
Lead II	-0.9	-0.4	-0.9
Lead III	-1.3	-0.9	-0.9
Lead IV	-3.0	-1.7	-4.0

*Electrocardiogram at rest after treatment with d.c.a. compared with electrocardiogram at rest before d.c.a.

†Electrocardiogram twelve minutes after adrenalin injection after pretreatment with d.c.a. compared with electrocardiogram twelve minutes after adrenalin injection before d.c.a.

‡Electrocardiogram two minutes after exercise after pretreatment with d.c.a. compared with electrocardiogram two minutes after exercise before d.c.a.

ALTERED EFFECT OF PHYSICAL EXERCISE

In six cases twenty genuflexions were performed before the first and twenty-four hours after the last d. c. a. injection. The reactions of the blood pressure immediately following exercise did not show any significant change (average increase 18 vs. 21 mm. systolic), and neither did the pulse rate (average increase 34 vs. 29 beats per minute).

Electrocardiograms were taken two minutes after exercise. In all instances there was an increased lowering or inversion of the T waves in at least two leads in the exercise electrocardiograms after pretreatment with d. c. a. as compared with those taken before the d. c. a. injections (Table II).

SUBJECTIVE SENSATIONS

In only two cases did there occur subjective sensations attributable to the treatment with d. c. a. In one case (Case 4) these consisted of precordial oppression on exertion (walking) which began on the third day of the d. c. a. treatment and disappeared again three days after the latter had been discontinued. In another case (Case 3) with marked enlargement of the heart there was some palpitation although the pulse rate was not significantly altered.

A marked intensification of the palpitation and dyspnea following the injection of adrenalin was observed in four of six cases pretreated with d. c. a. In two of six pretreated cases physical exercise (genuflexions) caused increased shortness of breath.

DISCUSSION

The most characteristic cardiovascular features observed after the administration of desoxycorticosterone acetate (d. c. a.) were an in-

crease of the diameter of the heart, changes of the electrocardiogram of the anoxic type, both at rest and after injection of adrenalin or after physical exercise, and a marked intensification of the effect of injected adrenalin upon the blood pressure.

A close interrelation of the suprarenal cortex and medulla is suggested by their morphological and vascular arrangement,^{31, 32, 33} by a parallelism of their vascular reactions to certain stimuli,³⁴ by chemical relations between cortical lipids and adrenalin,^{35, 36, 37, 38} by the fact that the administration of d. c. a. in the rat is followed by an accumulation of adrenalin-like substances in the heart, kidney and liver⁷ and by the intensification of the vascular effects of adrenalin through "Cortin."³⁹

The above-described observations on human beings are confirmatory of such a relationship. It appears possible that the effects of d. c. a. upon the heart and blood vessels are at least in part brought about by an increase of the secretion, deposition in the tissues and functional efficacy of adrenalin and related substances.

The blood pressure resting level was not significantly altered by the administration of d. c. a. while in patients with Addison's disease^{12-16, 24} and other conditions,²⁵ and in animals^{22, 23} hypertensive reactions have been observed after injections of d. c. a.

The enlargement of the heart which is the logical contrast to the diminution of the heart size in adrenal cortical deficiency^{3, 5-7} parallels that observed in Addison patients during treatment with d. c. a.²⁴

The regular early increase in body weight, which was obviously due to the retention of water, must not be interpreted as an indication of cardiac failure but rather as "edema of adrenal origin."²⁴

The appearance of "anoxic" changes of the electrocardiogram, chiefly affecting the T wave, both at rest and intensified after physical exercise and after injection of adrenalin, further stresses the similarity of the effect of d. c. a. with that of adrenalin.⁴⁰ It is in agreement with alterations of the T wave observed in dogs during treatment with d. c. a.¹⁸

While the subjective sensations of palpitation and dyspnea were increased in several of the persons pretreated with d. c. a. after physical exercise and after injection of adrenalin, there was one person who complained of angina-like symptoms during and after the treatment with d. c. a. alone. In this case there was also a moderate degree of tachycardia, a moderate elevation of the blood pressure level, and the greatest adrenalin sensitivity in regard to the reaction of the blood pressure after treatment with d. c. a.

The provocation of anginal symptoms through d. c. a. is reminiscent of analogous observations in persons treated with testosterone⁴¹ and it is well compatible with the theory that angina pectoris on effort is caused by the local anoxia-producing effect of adrenalin upon the myocardium.^{42, 43} It seems possible at least that this process of adrenalin anoxia of the heart muscle is also intensified by d. c. a., quite apart from the

fact that abnormally intense discharges of adrenalin into the blood stream immediately following physical exercise were found to be a characteristic of angina patients.⁴⁴

Most important appears the question whether or not d. c. a. as such or in combination with adrenalin plays any causal role in the pathogenesis of so-called "hypertensive" or "idiopathic" heart disease, particularly in those forms in which little or no coronary sclerosis is involved.⁴⁵ As pointed out in the introduction of this paper (items a-e) there exists a variety of clinical and experimental facts strongly suggestive of such a conception. It is further stressed by the results of the above-discussed experiments with desoxycorticosterone acetate in normal persons and by the presence of abnormally large amounts of adrenalin and adrenalin-like substances in the blood³⁰ and in the heart muscle¹⁷ of patients with congestive heart failure.

The mutual relationship between dilatation and hypertrophy of the heart on one side and abnormally high blood pressure on the other is not an obligatory one, as demonstrated by the experimental results discussed in this paper and by the not infrequently observed but seldom mentioned clinical cases of large hearts without hypertension and without coronary sclerosis. However, the same damaging agent which causes cardiac muscular hypertrophy and dilatation may cause in a similar way arteriolar muscular hypertrophy or arteriolar sclerosis and thus contribute to the elevation of blood pressure. Adrenalin-like compounds have been found in the tissue of arterial walls.¹⁷

The usual conception of "cardiac" edema as a merely physical phenomenon of hemodynamic and hydrostatic nature will probably require a thorough revision with consideration of the hormonal factors involved.

It should be re-emphasized that desoxycorticosterone acetate is only one of the "surprisingly large number of steroid derivatives of the adrenal cortex, many of which are physiologically active."²⁸ Its isolated effects as produced experimentally cannot possibly tell the whole story of the apparent hormonal pathogenesis of myocardial metabolic and structural pathology, but they are an impressive indicator of the fact that cardiology and endocrinology are beginning to overlap to an extent which would hardly have been thought of only a few years ago.

CONCLUSIONS

In healthy young men and in a patient with bronchial asthma the following effects of desoxycorticosterone acetate (Doca and Cortate) administered over periods of several days were observed:

1. Enlargement of the heart.
2. Anoxic changes of the electrocardiogram (persisting from few days to four weeks).
3. Moderate tachycardia or bradycardia.

4. Anginal complaints in one case.
5. Intensification of the effect of adrenalin upon the systolic blood pressure and of the accompanying subjective sensations.
6. Slightly increased anoxic changes of the electrocardiogram after injection of adrenalin and after physical exercise, as compared with the responses to the same stimuli before pretreatment with d. c. a.
7. Increase of body weight.
8. Increase of the relative concentration of blood adrenalin as compared with the amounts of other adrenalin-like substances.

The significance of the effects of cortical sterols and adrenalin upon the cardiovascular system is discussed in regard to the probable hormonal pathogenesis of the so-called "hypertensive" or "idiopathic" types of heart disease.

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THE AV_L , AV_R , AND AV_F LEADS

A SIMPLIFICATION OF STANDARD LEAD ELECTROCARDIOGRAPHY

EMANUEL GOLDBERGER, M.D.

NEW YORK, N. Y.

INTRODUCTION

STANDARD lead electrocardiograms, as Wilson, et al.,¹ have said, "may be regarded as a combination of two curves, each of which represents the potential variations during the cardiac cycle beneath a single electrode." In other words, the electrocardiograph, as routinely used, may be compared to a sphygmomanometer, which, instead of recording the actual systolic and diastolic levels of blood pressure, would merely indicate the difference between them (the pulse pressure). Because of this inherent defect, standard lead electrocardiography, despite its great value for almost forty years, has been limited. These limitations, in the main, are as follows:

1. Standard lead electrocardiograms are a composite of two equally important unipolar extremity leads¹ (the standard lead electrocardiogram is thus a bipolar extremity lead); whereas, in the case of precordial leads, the indifferent electrode records potentials which have but a minor influence on the electrocardiogram.

2. There is no constant relation between the direction of the deflection (upward or downward) and polarity. For example, an upward deflection in Lead I may represent five different combinations of polarity at that instant, namely,

- a. (-) potential at right arm (+) at left arm
- b. (-) potential at right arm (0) at left arm
- c. (-) potential at right arm (-) at left arm, but more (+) than right arm
- d. (0) potential at right arm (+) at left arm
- e. (+) potential at right arm (+) at left arm, but more (+) than right arm

3. The standard leads are taken according to the convention of Einthoven,² and precordial leads according to that of the American Heart Association.³

4. Standard leads cannot be directly compared with precordial leads.

To obviate these limitations, the use of leads which represent the potentials derived from only one extremity was naturally suggested.^{4a, b}

From the Department of Medicine, Lincoln Hospital, New York.

Presented as a preliminary report at the meeting of the New York Heart Association, New York Academy of Medicine, March 24, 1942.

Received for publication Oct. 6, 1941.

Unfortunately, not much progress was made in this direction because of difficulties encountered in obtaining a simple indifferent electrode of zero potential. (Although the Wilson assembly⁴ serves admirably, it is expensive and somewhat difficult to construct.) Fortunately, therefore, while studying extremity potentials, I was able to devise a very simple indifferent electrode of zero potential which can be constructed in the office in a few minutes.⁵ Further, since unipolar extremity potentials, as ordinarily derived, are small in amplitude and difficult to analyze, I devised a technique of obtaining augmented unipolar extremity leads in order to obviate this defect.⁵

The system of electrocardiography described below consists, then, of the use of the three augmented unipolar extremity leads (the aV- leads) and a precordial lead, as follows:

1. The aVl lead*—the augmented left arm extremity lead.
2. The aVr lead—the augmented right arm extremity lead.
3. The aVf lead—the augmented left leg extremity lead.
4. The V₄ lead, in which the electrode is placed in the fifth intercostal space at the mid-clavicular line.

For purposes of investigation, however, we are using the regular series of precordial leads, namely, V₁ to V₆.³

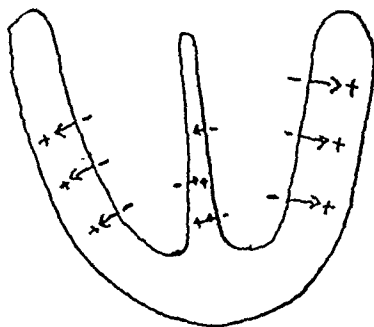


Fig. 1.—The spread of electrical activity in the ventricles. The arrows indicate the direction of spread, and the + and - signs, the relative polarities of the advancing wave of activity. The regression of electrical activity is not shown.

PHYSIOLOGIC PRINCIPLES UNDERLYING THE USE OF THE aV- LEADS

The potentials of the aV- leads vary directly with the electrical axis of the heart. This is true for both auricular and ventricular complexes. As a consequence, experimental observations on muscle strips and on the exposed heart are more or less directly applicable, as will be shown.

For our purposes in this paper, the following presentation of physiologic principles is adequate:

- a. Function in a tissue (for example, heart muscle) is associated with the production of differences of electric potential.⁷ Active muscle is relatively (-) to inactive muscle.

*The ordinary, unaugmented unipolar extremity leads are designated Vl, Vr, and Vf, respectively.⁶

b. No potential difference is produced by tissue within a zone of completely active, or completely inactive, muscle.^{8a}

c. The electrical forces produced by the heart, therefore, are derived from a transition zone of muscle, either undergoing activation or returning to the resting state.^{8a}

d. During activation, the side of the zone adjacent to the resting muscle elements (the direction in which the impulse is spreading) may be considered (+), and that adjacent to the active muscle elements as (-)^{8a} (Fig. 1).

e. Further, in the heart the zone may be considered in relation to the endocardium or epicardium. If the electrode is placed "facing" the endocardium, i.e., within the chambers of the ventricles^{8a} or over one of the large valvular orifices at the base of the heart, the potential will tend to be negative throughout the QRS complex, because the electrical impulse travels from within outward to the epicardium, and the endocardial surface remains relatively (-) to the epicardial^{8a} (Fig. 1).

f. Similarly, potentials derived from the right upper extremity are normally (-) because "the attachment of the right upper extremity to the trunk lies opposite the large valvular orifices at the base of the heart so that the right arm displays variations in potential similar to those that occur in the ventricular cavity."^{4b}

The aVr lead may therefore be considered as a quasi-intracardiac lead. In like manner, the precordial leads aVf and aVl (usually) may be considered quasi-extracardiac.

In this paper I have omitted discussion of the regression of electrical activity which produces the T wave.^{8b, 9}

TERMINOLOGY AND GENERAL REMARKS

The leads are always taken so that positivity is represented by an upstroke in the record. All measurements should be made in terms of millimeters, NOT millivolts. (In the aV- leads 1.5 cm. = 1 mv., whereas in the precordial leads, 1 cm. = 1 mv., although in both instances the galvanometer is standardized in the same way.⁵) (Fig. 2.)

P, T, and U waves are described as usual.

For the QRS complex the following situation holds: It must be emphasized that the QRS complex is a single entity, and that the only reason for separate identification of the individual waves is for purposes of description. With this in mind, I have complied with the desire of the American Heart Association to have a standard nomenclature applicable to all leads:

a. QS = an initial (-) downward deflection, if not followed by an upward deflection.

- b. Q = an initial (-) downward deflection, if followed by an upward deflection.
- c. R = the first upward (+) deflection.
- d. S = a downward (-) deflection, if present, following R.
- e. R' and R'' = additional upward (+) deflections after the first R.
- f. S' and S'' = additional downward (-) deflections after the first S.

To describe the relative sizes of the waves in a pattern, use small and capital letters, as, rS Qr, etc. (Fig. 2.)

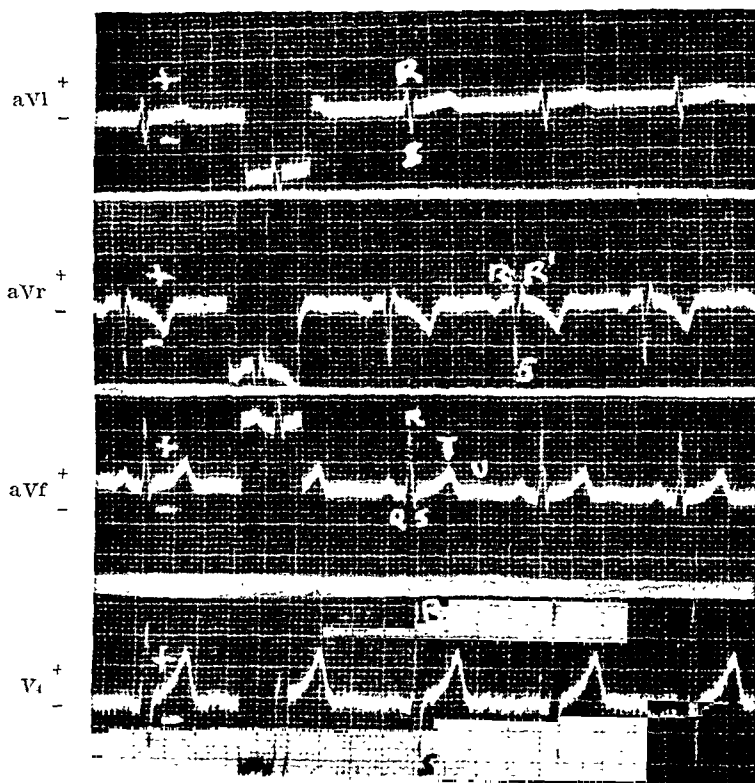


Fig. 2.—Normal male, aged 28 years. In both aV- and precordial leads the standardization mark rises or falls 1 cm.⁵

NORMAL RECORDS

Normal values for the amplitudes of individual waves are presented in Table I. The mathematical relations between standard and unipolar extremity leads are shown in Appendix A. In Fig. 2 a normal record is shown.

The aVl lead.—Unlike the aVr or the aVf leads, there is no basic normal pattern for any of the waves. P, though usually (+), may be (-). The main ventricular deflection and T are usually (+). Occasionally the aVl lead resembles the aVr lead and QRS and T are (-) (Fig. 3a).

The aVr lead.—There is a basic normal pattern of the aVr lead, consisting of a (–) P; a monophasic (–) QS; an isoelectric RS-T interval; and a (–) T (Fig. 2). Either R or both R and R' may be present (Fig. 3b).

The aVf lead.—The basic pattern of the aVf lead is just the reverse of the aVr lead; there are a (+) P; a monophasic (+) QRS, comprising only an R; and a (+) T. Either Q or S, or both, may be present (Fig. 3c).

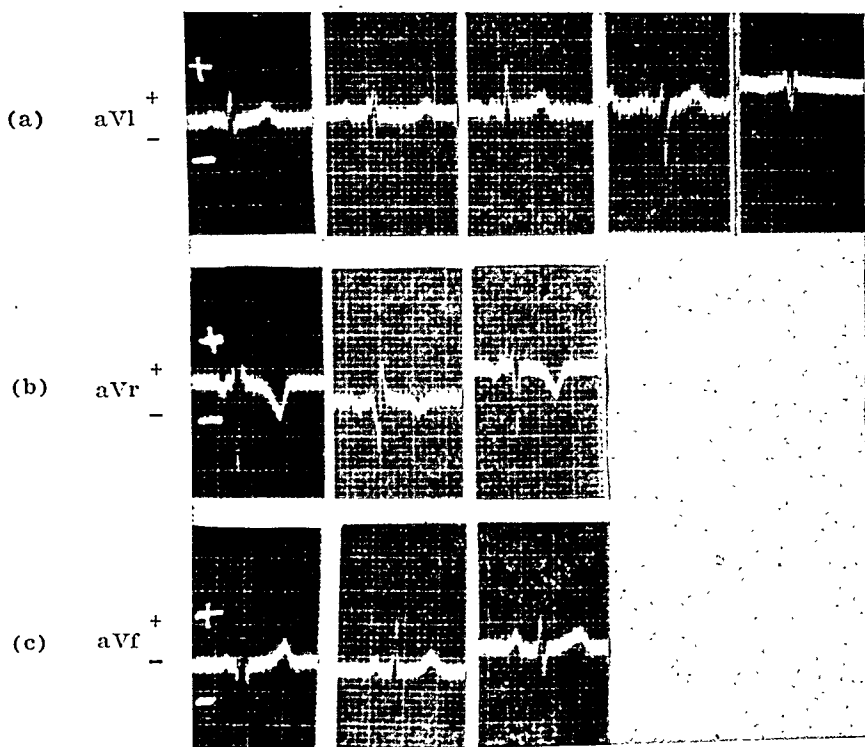


Fig. 3.—Examples of normal variations in the aV- leads. Each of the eleven records is from a different case.

AURICULAR PATTERNS

As was previously mentioned, the potential (shape) of the P wave in the aV- leads varies directly with the electrical axis of the auricular muscle. Since in the auricle the electrical axis corresponds closely to the actual path of the spread of the impulse, the shape of the P wave in the aV- leads offers a good clue as to the actual path of the impulse.

This is well illustrated in the case of auricular flutter. Although in standard leads the flutter waves appear to be composed of a short, followed by a long, stroke,¹⁰ the fact that the impulse travels clockwise over a 360° path has long been well established.¹⁰ If the aV- leads are used and the electrical axis for one complete auricular cycle is calculated, it will be seen that the pattern in auricular flutter is a modification of a sine curve (Fig. 4). Similarly, nodal rhythm, ectopic auricular impulses, etc., may be analyzed.

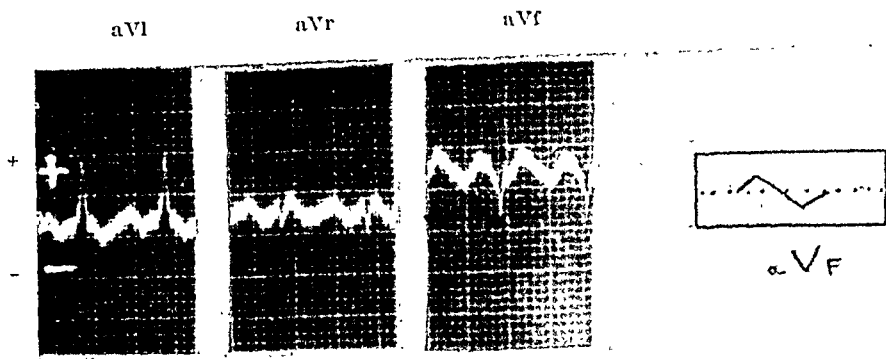


Fig. 4.—Auricular flutter. The small box at the right shows one complete auricular cycle in the aVF lead. It should be pointed out that, since there is a "circular movement" in operation, the points representing the beginning and end of the cycle are arbitrary. The presence of a deep Q in the aVF lead indicates myocardial damage.

VENTRICULAR PATTERNS

Without attempting to cover the entire field of electrocardiography, the basic patterns in axis deviation and ventricular hypertrophy, acute myocardial infarction, coronary insufficiency, pericarditis, and pulmonary embolism, and the electrocardiographic changes caused by the administration of digitalis will be described briefly.

Axis Deviation and Ventricular Hypertrophy.—It may be stated as axiomatic that the potentials of the aVL, aVR, and aVF leads are functions of the electrical axis of the heart, and further, that the algebraic sum of the potentials of these three leads, at a given instant, always equals zero. This is graphically illustrated in Fig. 5. The diagonal

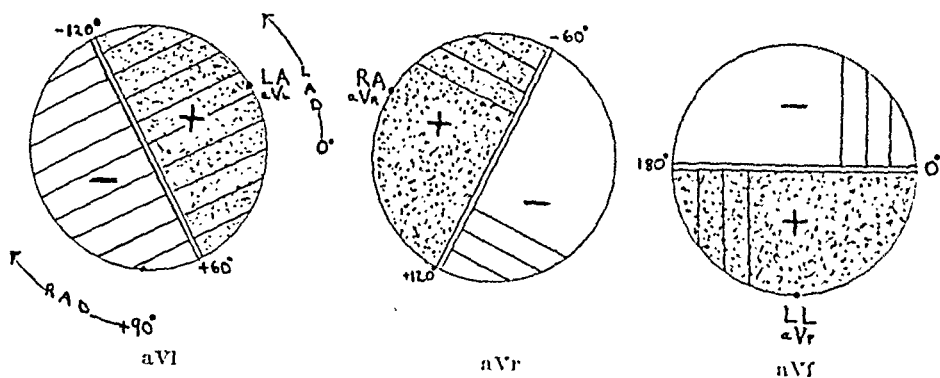


Fig. 5.—Graphs illustrating the relationships between the potentials and polarities of unipolar extremity leads and the electrical axis.

The diagonal and vertical lines indicate how the amplitudes of the records vary. In the diagrams, not all of the oblique and vertical lines were drawn.

In the aVL lead when angle α changes from $+59^\circ$ to $+61^\circ$, the polarity of the auricular or ventricular deflection becomes - instead of +, and vice versa; when angle α changes from -119° to -121° , the polarity of the auricular or ventricular deflection becomes + instead of -, and vice versa.

In the aVR lead when angle α changes from -59° to -61° , the polarity of the auricular or ventricular deflection becomes + instead of -, and vice versa; when angle α changes from $+119^\circ$ to $+121^\circ$, the polarity of the auricular or ventricular deflection becomes - instead of +, and vice versa.

In the aVF lead when angle α changes from $+1^\circ$ to -1° , the polarity of the auricular or ventricular deflection becomes - instead of +, and vice versa; when angle α changes from -179° to $+179^\circ$, the polarity of the auricular or ventricular deflection becomes + instead of -, and vice versa.

and vertical lines illustrate how the QRS complex becomes larger or smaller with changes in the electrical axis.

With respect to axis deviation, by definition, left axis deviation exists when Einthoven's angle α passes 0° and becomes $(-)$; and right axis deviation, when the angle α passes $+90^\circ$ in a clockwise fashion and becomes more $(+)$.

To consider Fig. 5 for a moment again. Although the potentials of all three unipolar extremity leads vary with the electrical axis, the aVl lead seems to show these variations best, because as 0° is passed counterclockwise, the $(+)$ potentials tend to increase in amplitude; and as $+90^\circ$ is passed clockwise, the $(-)$ potentials tend to be augmented. The use of the left arm lead as a measure of axis deviation, however, is not original with me; Wilson, et al.,⁶ and Kossmann and Johnston^{4b} previously suggested it. *Therefore, as a general rule, an upward aVl lead potential represents left axis deviation; and a downward main aVl deflection, right axis deviation.*

In the event that it is desired to calculate the actual angle of the electrical axis of the heart (Einthoven's angle α), it will be necessary to make use of special tables which I compiled but which are omitted in this paper.

The Electrocardiographic Patterns of Left Axis Deviation and Left Ventricular Hypertrophy.—The patterns have arbitrarily been divided into four types, 1° , 2° , 3° , and 4° . From the graphs in Fig. 5, one would expect the first sign of left axis deviation to be a change in the polarity of the aVf lead from $(+)$ to $(-)$ (1°). Then, with increased axis deviation (2°), the aVr potentials should become increasingly smaller, until an angle of -60° is reached, when they should change and become $(+)$.

In the aVl lead, left axis deviation should produce a heightened QRS until -30° is reached, when the potential should begin to decrease. Actually, this occurs (Fig. 6). However, when 2° left axis deviation becomes marked, signs of ventricular hypertrophy also appear (see below). The patterns of left axis deviation are described in Table II.

TABLE I
NORMAL VALUES IN THE aV- LEADS

	aVl		aVr		aVf	
	MIN. (MM.)	MAX. (MM.)	MIN. (MM.)	MAX. (MM.)	MIN. (MM.)	MAX. (MM.)
P	-1	+1.5	-0.4	-2	0	+2.5
Q	0	-2	-2	-17	0	-3
R	+1	+10	0	+1.8	+1.2	+20
R'	0	+2	0	+4	0	+5
S	0	-8	0	-17	0	-6.8
S'	0	-2	--	--	0	-1.5
T	-1*	+1.5	-0.8	-3.5	0	+4
U	0	+0.5	0	-0.5	0	+0.5

*In the aVl lead, a $(-)$ T is to be considered normal only if an rS pattern exists, or if the major QRS deflection is $(-)$ so that the ventricular complex resembles that of the aVr lead.

Left Ventricular Hypertrophy.—With ventricular hypertrophy, unlike axis deviation, T-wave changes appear, and T points in a direction opposite to that of the main ventricular complex.

With the left ventricular hypertrophy, concomitant right ventricular hypertrophy may also occur, and the resultant electrical axis may approach normal, but the T-wave changes will be present.

Considering the QRS patterns, Barnes¹² has described two types of electrocardiographic patterns in cases of hypertensive cardiovascular disease, under the title "Chronic Left Heart Strain." In one, Lead II is similar to Lead I (Fig. 6*d*); in the other, Lead II is similar to Lead III (Fig. 6*c*). In the unipolar extremity leads, the main point of difference between these two patterns is in the aVr lead. When Leads II and I are similar, the main aVr deflection is deeply (-); in the type in which Leads II and III are similar, the main aVr potential has become (+).

TABLE II

THE ELECTROCARDIOGRAPHIC PATTERNS OF LEFT AXIS DEVIATION AND VENTRICULAR HYPERTROPHY

		1° LAD	2° LAD	3° LVH	4° LVH
		Angle α near 0°	Angle α (-)	Angle α less (-) than -60°	Angle α more (-) than -60°
aVl	QRS T	+ :q may be present +	Same as 1°	+ :q may be present -	Same as 3°
aVr	QRS T	- -	Same as 1°	- +	QR -
aVf	QRS T	rSr or rSr's' +	rS +	rS +	Same as 3°

TABLE III

THE ELECTROCARDIOGRAPHIC PATTERNS OF RIGHT AXIS DEVIATION AND VENTRICULAR HYPERTROPHY

		1° RAD	2° RVH	3° RVH
		Angle α more (+) than 90°	Angle α less (+) than +120°	Angle α more (+) than +120°
aVl	QRS T	- :rS + may be (-)	- :rS +	Same as 2°
aVr	P QRS T	- - -	Often large and notched - +	Same as 2° QR -
aVf	P QRS T	+ + :q may be present +	Often large and notched + -	Same as 2°

From Fig. 5 we learn that when the angle α passes from -59° to -61°, the potential at the aVr lead changes from (-) to (+). The value for angle α in Fig. 6*d* is -5°,* and in Fig. 6*c*, -70°.* In other words, Fig.

*By actual calculation.

6c represents merely a greater degree of axis deviation than Fig. 6d. The characteristics of these types are described in Table II.

Still another type of electrocardiographic pattern is found in certain cases of ventricular hypertrophy. Some of the features of left ventricular hypertrophy, and some which are attributable to right ventricular hypertrophy, are seen (Fig. 9a).

Right Axis Deviation and Right Ventricular Hypertrophy.—These patterns have been divided into three types, 1°, 2°, and 3°. Study of Fig. 5 reveals that an increase of right axis deviation will produce larger (–) aVl potentials. In the aVr lead, the amplitude of the (–) deflections should decrease until +120° is reached, when the main deflection becomes (+). In the aVf lead, the main deflection is always (+) (Fig. 6).

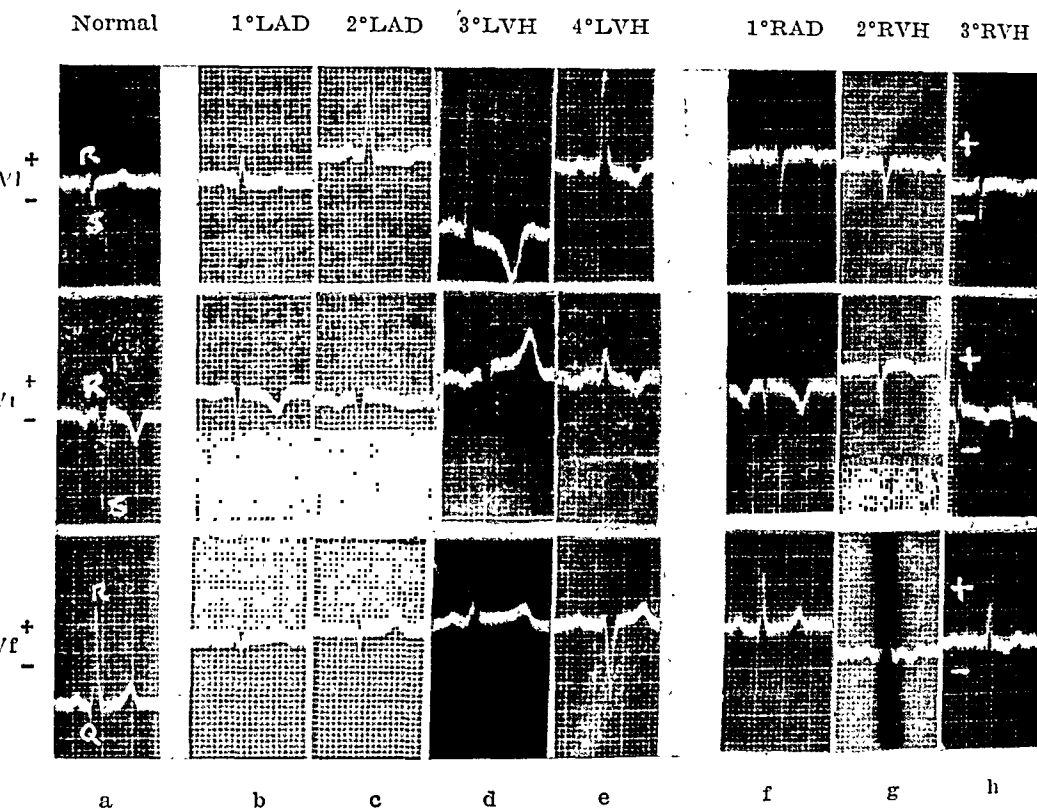


Fig. 6.

Fig. 6.—Electrocardiographic patterns of axis deviation and ventricular hypertrophy. a, Normal; b, left axis deviation 1°; c, left axis deviation 2°, the (–)T aVl is indicative of some degree of ventricular hypertrophy; d, left ventricular hypertrophy 3°; e, left ventricular hypertrophy 4°; f, right axis deviation 1°; g, right ventricular hypertrophy 2°; auricular fibrillation; h, right ventricular hypertrophy 3°; auricular fibrillation.

Right Ventricular Hypertrophy.—Here, again, Barnes¹² has described two types, one in which Leads I and II are similar (Fig. 6g), and another in which Leads II and III are similar (Fig. 6h).

In the unipolar extremity leads, again the main point of difference is in the aVr lead, and is caused by the degree of axis deviation. Fig. 6g represents an almost normal angle α (this is due in part to concomitant

left ventricular hypertrophy and rotation of the heart around its longitudinal axis). In Fig. 6h there is marked axis deviation.

The characteristics of right axis deviation and ventricular hypertrophy are presented in Table III.

Acute Myocardial Infarction.—When one of the coronary vessels is occluded, tissue anoxemia and death occur, and certain physiologic changes take place, irrespective of the location of the infarct.

First, a current of injury is produced. This is *not* observed in the electrocardiogram because its effect is neutralized during standardization (Fig. 7).

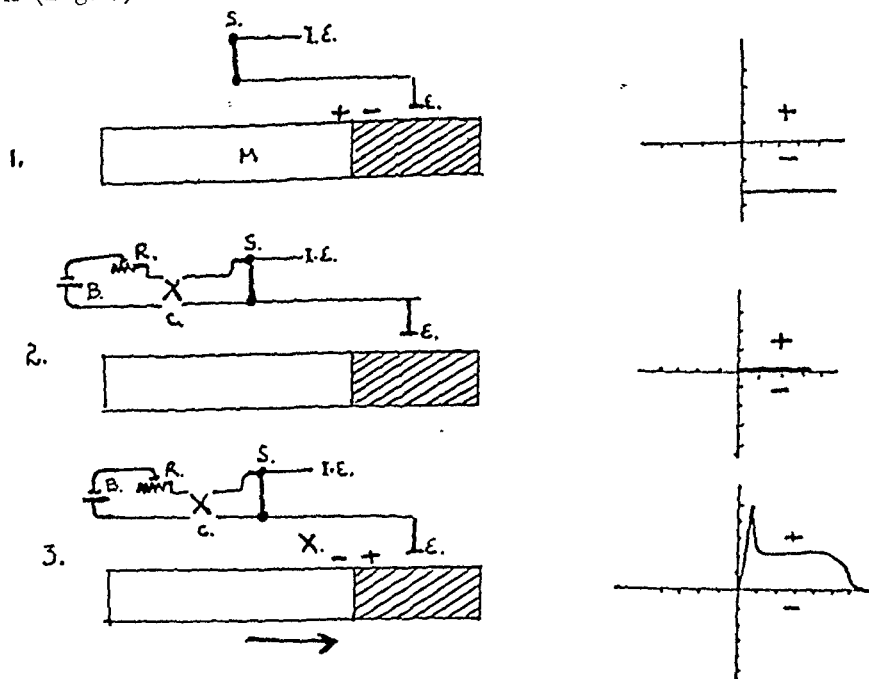


Fig. 7.—Diagram showing how current of injury is neutralized. *E*, Electrode; *I.E.*, indifferent electrode; *M*, strip of muscle immersed in a medium of uniform and extensive conductivity; *S*, galvanometer string; shaded area represents injured (or dead) muscle; + or - signs represent polarity as impressed on the string; *C*, current reverser; *B*, battery; *R*, variable resistance; arrow indicates direction of spread of impulse. 1, Shows current of injury; 2, shows how current of injury is neutralized with a battery, variable resistance and current reversing switch; 3, shows type of electrogram obtained by passage of an impulse through the muscle strip from left to right. An electrode at *x* would record a (-) RS-T deviation.

Second, there are RS-T changes, for the following reason: as the electrical impulse enters the dying and dead area, the excitation wave is blocked because it cannot penetrate the injured tissue. The potential difference at this boundary between vital and injured tissue is, therefore, the cause of the RS-T segment deviations (Fig. 7). Whether the RS-T deviation will be (+) or (-) depends solely on the relation of the electrode to the infarcted area. A unipolar lead which overlies or faces the infarcted region will record a (+) RS-T deviation; one which faces the normal surrounding tissue, a (-) RS-T deviation (Fig. 7).

Third, T-wave changes occur as a later phenomenon. The T wave develops in a direction opposite to that of the RS-T deviation, and

occurs coincident with the regression of the RS-T deviation. (The reason for this will be described elsewhere.)⁹

Fourth, Q waves may also develop coincident with the RS-T deviations in leads overlying or facing the infarct, for the following reason: Normally as the excitation wave spreads out toward the epicardium, the precordial electrode faces the oncoming impulse and the initial deflection will be (+) (see Fig. 1). With infarction, there is no impulse, and an electrode overlying the infarct may be considered as facing the endocardium whose potential is (-). Thus, the initial deflection is (-), or a Q wave. It is as if a hole were cut in the ventricular wall and the electrode were placed over it.

In considering the subject of anterior and posterior infarcts, it should be emphasized that it is the location of the infarcted area, *not* the particular artery which has been thrombosed, that determines the electrocardiographic pattern.

Anterior Infarcts.—With infarcts of this type, the regions affected may include the anterior portion of the left ventricle, the adjacent portion of the interventricular septum, and the apex.¹²

The electrocardiogram in a typical case is illustrated in Fig. 8. The outstanding features of this pattern are:

<i>aVl lead</i>	QRS: A deep Q (which is the cause of the Q_1 of standard leads) and a prominent final R are present
	RS-T: +
	T: Later becomes (-) as the RS-T deviation regresses
<i>aVr lead</i>	QRS: Normal; occasionally a final R or R' may appear
	RS-T: (-), usually inconspicuous
	T: (+)
<i>aVf lead</i>	QRS: Normal
	RS-T: (-)
	T: (+)

There is a reciprocal relation between the RS-T deviations and the T waves of the aVl and aVf leads. Precordial leads are described in Fig. 8. The explanation for these patterns is as follows: Precordial leads and the aVl lead overlie or face the infarct, which involves the antero-lateral wall of the left ventricle,¹⁵ and so record an initial (-) deflection, the Q, and a (+) RS-T. A Q (aVl), therefore, is more significant than a Q_1 . The aVr and aVf leads, facing the surrounding vital tissue, record a (-) RS-T, and QRS is essentially normal.

It may be pointed out that, if a small area is infarcted, an electrode placed directly over the infarcted zone will record normal deflections up to the moment the impulse reaches the infarct and becomes blocked, causing the RS-T deviation. However, if the experimental infarct is made sufficiently large (as occurs in man), the initial (+) deflection disappears.^{13b, 14}

When the anterior infarct is small or atypical, the standard leads may be equivocal or normal, and the only evidence may be present in the

aVI lead, in which the RS-T segment is characteristically flattened and T coved (Fig. 10a).¹⁰

Posterior Infarcts.—Electrocardiograms of this type are produced by infarction of a region which may include the posterior basal portion of the left ventricle and the adjacent portion of the interventricular septum.¹² This region, as Wilson has pointed out,² overlies the diaphragm and is *inferior* rather than *posterior*.

Anterior Infarction				Posterior Infarction			
		Later T				Later T	
	QRS	RS-T changes	Fig.		QRS	RS-T changes	Fig.
aVI ⁺	Q	+	-			-	+
aVr ⁺		-	+		r	-	+
aVf ⁺		-	+		Q	+	-
v ₁ ⁺	Q	+	-			-	+

Fig. 5.—Typical electrocardiographic patterns observed in cases of *anterior* myocardial infarction. The record of anterior infarction was taken on the fourth hospital day; that of the posterior infarction, two weeks after the attack.

A typical electrocardiogram is shown in Fig. 8. The significant features of this pattern are:

- aVI lead QRS: Normal
- RS-T: (-)
- T: (-)
- aVr lead QRS: Normal. An initial R* is often seen
- RS-T: (-) inconspicuous
- T: (+)
- aVf lead QRS: Deep Q*
- RS-T: (+)
- T: (-)

*It is the Q of the aVf lead which is the cause of the Q_r. When present, the R of the aVr lead contributes to the Q_r. (Appendix A.)

As with anterior infarcts, there is a reciprocal relation between the RS-T deviations and T waves of the aVl and aVf leads.

Precordial leads are described in Fig. 8. When there is a small or atypical posterior infarct, standard leads may be normal, and the only evidence may be present in the aVf lead, which will show a small QRS with a Q and coronary T wave (Fig. 10b).¹⁹

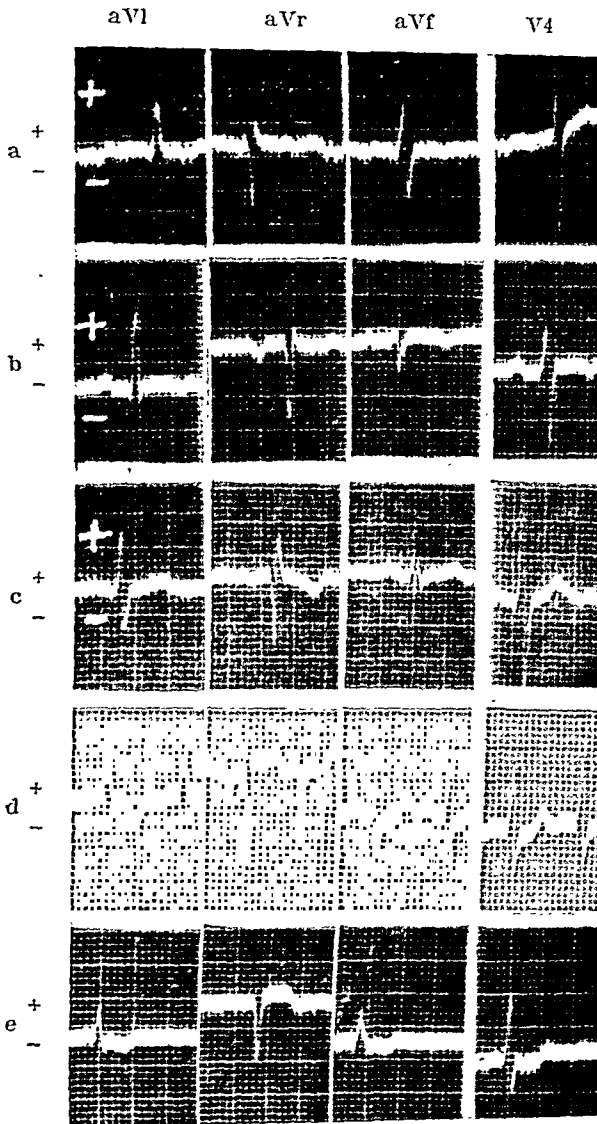


Fig. 9.—*a*, Atypical left ventricular hypertrophy, male, aged 44 years. Auricular fibrillation and digitalis effects. The deep S (aVf) makes the pattern atypical. *b*, Acute pericarditis (acute rheumatic fever), male, aged 32 years. Note the dome-shaped RS-T in the aVl, aVf, and V4 leads. In the aVr lead, T is (+). *c*, Mild pulmonary embolism, male, aged 43 years. Four days after embolism. Standard leads showed an S₁ Q₃ pattern. *d*, Acute coronary insufficiency, female, aged 52 years. The patient died seven hours after record was taken, still in shock. The (-) T in the aVl lead is often observed. *e*, Digitalis effect, female, aged 63 years. Hyperthyroidism-auricular fibrillation.

Multiple Infarcts.—It is not always a simple matter to ascertain exactly what region has been infarcted for a variety of reasons. A new infarct may occur in a previously damaged heart, in which case electrocardiographic signs of the old infarct in the form of Q-wave changes

are often permanent. Again, the heart may be the seat of multiple, acute infarcts, in which case the reciprocal relations between aVl and aVf patterns are lost; or a complicating pericarditis may also obscure the picture.

Pericarditis.—There appears to be general agreement that the electrocardiographic changes in most instances of pericarditis are an expression of an associated subepicardial myocarditis.^{10a, b} It is this, and *not* the presence of pericardial effusion, which is the cause of the RS-T segment deviation. A typical pattern is pictured in Fig. 9b.

The cause of the RS-T deviation is the same as in myocardial infarction. The damaged subepicardial tissue produces a slight block of the impulse. Leads from the surface of the heart, as the aVl lead, the aVf lead, and precordial leads, show, therefore, a (+) RS-T deviation and (−) T; and leads which “face” the endocardium, as the aVr lead, a (−) RS-T deviation and (+) T. These typical patterns are not always observed in all leads, however, depending on whether the pericarditis is localized or diffuse.

*Acute Coronary Insufficiency.*¹⁰—Acute coronary insufficiency provoked by a disproportion between the oxygen requirements of the heart and the coronary blood flow results in focal areas of myomalacia, largely subendocardial, without affecting the larger coronary arteries.¹¹ The electrocardiographic pattern, determined by the subendocardial localization of the muscle injury, is briefly as follows (Fig. 9d): The aVr lead, facing the injured endocardial area, records a (+) RS-T deviation. The aVl, aVf, and precordial leads, facing the surrounding vital tissue, record (−) RS-T deviations. Abnormal Q waves are not observed. The aVr lead normally presents a Q wave.

A similar pattern is often present during a seizure of angina pectoris due to acute, but temporary, myocardial ischemia. In cases of angina, I have also observed electrocardiographic evidence of myocardial damage in aV—leads, even at rest, when the standard leads were normal.⁹

Nonspecific Myocardial Injury.—Aside from coronary artery thrombosis and acute coronary insufficiency, there are a wide variety of conditions which may injure the myocardium, such as acute rheumatic fever, acute infectious diseases, severe anemia, and trauma. Without describing these in detail it may be stated that the location and extent of the injury, rather than the nature of the noxious agent, determine the electrocardiographic pattern.

Pulmonary Embolism.—“It would appear that the electrocardiographic pattern following pulmonary embolism is a classic example of changes due to unilateral (right) ventricular strain.”¹² The changes observed, however, are variable,¹⁷ and may include those pictured in Fig. 9c. In this record, the RS-T deviations which are so often seen did not occur. RS-T deviations, when present, are due to an associated

acute coronary insufficiency (see above). It may be observed that here the Q_s is written by the aVl lead, *not* the aVf lead, as in myocardial infarction (Fig. 9c).

*Digitalis Effects.*⁹—The effects of digitalis on the electrocardiogram depend to a certain extent on the pattern prior to the administration of the drug. In general, the following changes occur in the ventricular complex of aV- leads:

1. A decreased Q-T or RS-T interval.
2. RS-T deviation in a direction opposite to that of the T wave.
3. Decrease in the amplitude of the T wave. When maximal, there are complete reversal of polarity and fusion with the RS-T segment (Fig. 9e). In this connection it should be borne in mind that RS-T deviations and T-wave changes may also be caused by adrenalin, insulin, and other drugs and functional conditions, such as postural hypotension.¹⁸

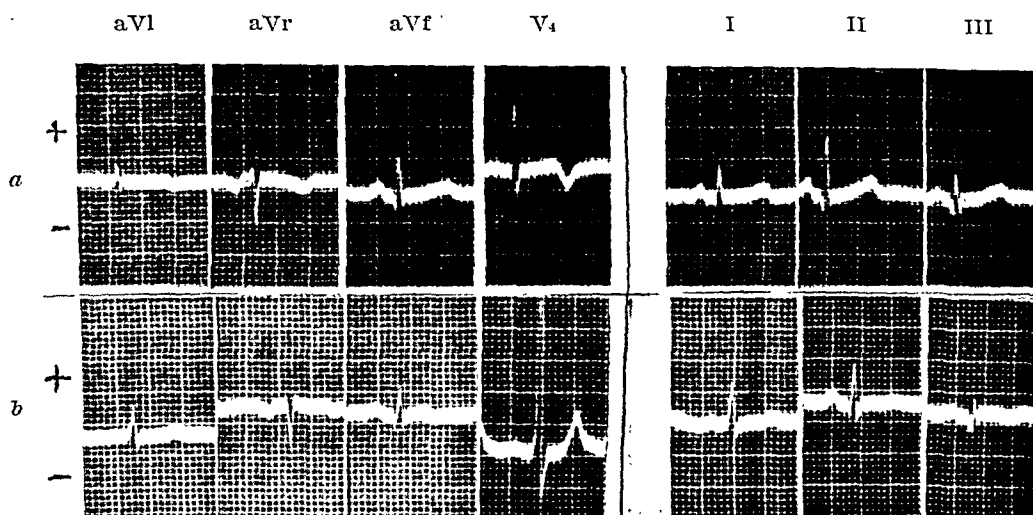


Fig. 10.—Atypical myocardial infarction. *a*, Anterior infarct, male, aged 41 years, two days after attack. Standard leads are normal. Lead V_4 is abnormal. The flattened RS-T and coronary T of the aVl lead are typical and characteristic. *b*, Posterior infarct, female, aged 53 years, one week after attack. Standard leads show equivocal T-wave changes. Lead V_4 is within normal. The q and coronary T of the aVf lead are characteristic of an atypical posterior infarct.

DISCUSSION

As with standard leads, the use of this system of “augmented” unipolar extremity leads is predicated on acceptance of the Einthoven triangle concept. Without going into a detailed discussion of the validity of this hypothesis, I will say that the fact that “augmented” unipolar extremity electrocardiograms may be obtained with either my or Wilson’s indifferent electrode is, for practical purposes, proof of the applicability of this concept. Further, the calculation of the angle α in standard leads is dependent on this very concept.

Justification for the introduction of a “new” system of electrocardiography (if justification is necessary) is that the system I have presented is NOT new in the sense that the principles underlying its use

are identical with those governing standard leads. In fact, I might go so far as to say that the standard leads, rather than the unipolar extremity leads, were originally used because no technique existed in Einthoven's time by which a standard lead potential could be separated into its two component unipolar extremity lead potentials. It cannot be too strongly emphasized that a standard lead represents a combination of the potentials of two unipolar extremity leads,¹ and not the converse.

CONCLUSIONS

The outstanding features of the aVL, aVR, and aVF leads are as follows:

1. Since they are essentially unipolar extremity leads, they record potentials from only one region of the body, unlike the standard leads, each of which represents the combined potentials of two unipolar extremity leads.

2. In fact, the relation between the augmented unipolar extremity leads and standard leads is fixed, and may be expressed mathematically (Appendix A).

3. Positivity and negativity have definite significance when correlated with the actual electrical phenomena in the heart for both the aV- leads and the precordial V- leads. Further, in accordance with mathematical principles, positivity is always represented by an upward deflection.

4. The aVL, aVR, and aVF leads are so related that the algebraic sum of their potentials (at the same instant) equals zero.

5. Each of the aV- leads may be interpreted in relation to the others, or to precordial, esophageal, or any leads taken with an indifferent electrode of zero potential.

6. The potentials of the aV- leads vary directly with the electrical axis of the heart:

7. Since the same electrical phenomena produce unipolar extremity and bipolar standard leads, the patterns that have in the past been described in the standard leads may now be seen and analyzed in a clearer, uncombined form. In fact, the standard leads must be considered as complicated unipolar extremity leads.

8. An important clinical advantage of augmented unipolar extremity leads over standard leads lies in the diagnosis of coronary artery disease. For example, in a case of myocardial infarction, when the standard leads are normal, characteristic RS-T deviations and T-wave changes will occur in one or more of the aV- leads. Also, in angina pectoris, at rest, evidence of myocardial damage may be observed in aV- leads even when the standard leads are normal.

In the preceding pages I have in a broad and general way described the physiologic bases for the more important electrocardiographic

patterns, and their direct application to the aVl, aVr, and aVf leads, both normal and abnormal. With these leads, the patterns not only of the normal electrocardiogram, but also of axis deviation and ventricular hypertrophy, assume a logical sequence for the first time. This is to be expected, inasmuch as the QRS patterns are direct functions of the electrical axis.

In this system, the physiology of the RS-T segment deviations which have been previously described in acute myocardial infarction^{13a} becomes directly applicable, which is impossible with standard leads. The same holds for the RS-T patterns of pericarditis, angina pectoris, coronary insufficiency, and pulmonary embolism.

Again, the full significance of Q₁, and especially Q₃, becomes apparent when these deflections are analyzed as component parts of unipolar extremity leads.

Although I did not elaborate upon it in this paper, the effects of digitalis on the RS-T segment and the T wave may be shown to follow a logical sequence, not only in the unipolar extremity leads, but also in precordial leads.⁹

However, the final word has not been written, either on the relation of the aV- leads to electrocardiographic physiology, or on their multi-fold patterns and interpretation. Many problems await solution; but I will say that study and use of these leads, especially at first, in conjunction with standard leads, will lead to a fuller understanding of not only standard leads and of the aV- leads and precordial leads, but also of the physiologic principles underlying electrocardiographic patterns.

Finally, the fund of knowledge that has been accumulated with the standard leads will NOT be lost with the use of this technique; rather, in transcribing it in terms of the aV- leads (using the equations in Appendix A), a more rational concept of the significance of this knowledge may be obtained.

I wish to express my appreciation to Dr. Frank N. Wilson, Ann Arbor, Mich., for his many helpful suggestions on terminology, and on the preparation of this paper; Doctors Leander H. Shearer, Frederick H. Howard, and Harry Greisman, of the Department of Medicine, and Dr. Alexander W. Kruger, Medical Superintendent, and Dr. Marcus Schramm, for their cooperation; and to the many others on the interne and nursing staff of the Lincoln Hospital, who so kindly assisted me in obtaining and selecting material.

APPENDIX A

Relationship of Augmented Unipolar Extremity and Standard Leads.—The value of potentials at the right arm, in terms of standard lead potentials, may be expressed by the equation:

$$RA = - \frac{I + II}{3} \quad 6 \quad 1$$

In the above equation, it is simpler to consider an upward deflection in the standard leads as (+), and a downward deflection as (-). For this reason, Lead I will

have to be considered as LA minus RA, and Lead II as LL minus RA. (The reason for this is that, in Lead I, both a (-) potential of RA and a (+) potential of LA produce an upward deflection; and similarly, in Lead II, both (-) RA and (+) LL potentials produce an upward deflection. In Lead III an upward deflection is produced by (-) LA and (+) LL potentials.

Equation 1 may, therefore, be rewritten:

$$RA = - \frac{(LA-RA) + (LL-RA)}{2} \quad 2$$

or

$$= - \frac{LA + LL - 2RA}{2} \quad 3$$

Now $RA + LA + LL = 0$
Therefore, $LA + LL = -RA$
and equation 3 becomes:

$$\begin{aligned} RA &= - \frac{-RA - 2RA}{2} \\ &= - \frac{-3RA}{2} \\ &= RA \end{aligned}$$

Since the aVr lead $3/2 RA$,
equation 1 becomes:

$$aVr = - \frac{I + II}{2}$$

Similarly,

$$aVI = \frac{I + III}{2}$$

and

$$aVf = \frac{II + III}{2}$$

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TREATMENT OF EDEMA WITH AN ORALLY ADMINISTERED MERCURIAL DIURETIC

JOSEPH F. BORG, M.D.
ST. PAUL, MINN.

IN THE treatment of many patients with edema, mercurial diuretics are today regarded as indispensable. There have been a number of successive compounds, each of which possessed distinct advantages over its predecessor, but all have had the disadvantage of requiring parenteral administration. This usually necessitated intravenous injections often enough to maintain an edema-free state. Minor, but uncomfortable, toxic effects have occurred frequently, especially in older people. It was found that these could be avoided by giving smaller and more frequent doses. Obviously this is a definite drawback from the economic aspect, and also predisposes to thrombosis of the veins, which is a disadvantage when medication must be carried out over a considerable time. These facts stress the importance of securing an effective preparation for oral administration.

The most satisfactory diuretics of this series have been markedly improved, with increased effectiveness and lessened toxicity, by combining them with theophylline. It has been shown by Chrometzka,¹ Saxl,² and Görl³ that this combination can be safely and effectively used by mouth. Batterman, DeGraff, and Rose⁴ reported on the use of an oral preparation in comparison with an intravenous preparation of the same material. They used an arbitrary dose for twenty-nine patients at variable intervals over a relatively short period, and reported that the preparation was safe and effective. Blackford⁵ reported favorable results in four cases.

This report is concerned with the use of oral tablets of a complex mercury compound, sodium salicyllallylamide-o-acetate, in part a chemical combination, in part a mixture, with theophylline (salyrgan-theophylline tablets). They have been used over a period of twenty months in a series of thirty-nine patients. Twelve were hospital patients, fourteen were patients in an outpatient cardiac clinic, and thirteen were ambulatory private patients. Most of them had long been under care for chronic myocardial insufficiency, and had received various diuretics.

METHOD

Patients with edema associated with the diseases listed in Table I were treated. Those with cardiac disease had heart failure, and were receiving therapeutic doses of digitalis. All of the patients received 6 Gm. of ammonium nitrate daily, start-

Received for publication Feb. 14, 1942.

ing at least two days before the administration of the salyrgan-theophylline tablets was begun. No other medication was used except sedatives, as indicated. Hospital patients were kept strictly in bed. Intake and output records were kept in many cases, but, on the whole, proved much less reliable in estimating the results of diuresis than weighing the patients daily under constant conditions. This was done before breakfast, after emptying the bladder, with the patient wearing the same clothing, and using the same scales. Only those patients who had maintained a constant weight for several days were included. The preparation used was an investigational product of salyrgan-theophylline in the form of tablets for oral administration (STO). Each tablet contained 0.08 Gm. of salyrgan and 0.04 Gm. of theophylline. This represented 0.03168 Gm. of mercury per tablet.

TABLE I

DIAGNOSIS	NO.	RESULTS			TOXIC EFFECTS
		GOOD	FAIR	NONE	
Mitral Stenosis	8	5	1	2	2
Hypertension	14	10	3	1	6
Coronary Sclerosis	8	7	0	1	3
Cirrhosis of the Liver	3	2	0	1	1
Aortic Stenosis	2	2	0	0	1
Syphilitic Aortitis	1	1	0	0	0
Phlebitis—Legs	1	0	1	0	0
Ca. Ovary	1	0	0	1	0
Ca. Rectum	1	1	0	0	1
Total	39	28	5	6	14

The results are recorded in Table II. "Good" includes those patients who obtained marked relief from their edema, as indicated by a persistent weight loss and increased urinary output. "Fair" includes a group of patients who, with the initial dose, lost no weight and had no significant increase in urinary output. These patients, however, did respond to intravenous injections of salyrgan-theophylline, after which the edema was prevented from recurring by the use of the STO tablets. "None" includes those who fell in neither of the previously described groups.

The urine and blood were watched for toxic effects, and the patients were carefully questioned about toxic subjective manifestations. Under the heading, "Initial Weight Loss," data are given to show the maximal diuretic effect of the tablets in terms of weight loss, and the time and number of tablets necessary to obtain it. "Total Time" indicates the length of the period of observation over which the salyrgan-theophylline was given, not necessarily continuously. "Total Tablets" shows the number of salyrgan-theophylline tablets which were used during the "Total Time."

OBSERVATIONS

Most of the patients had been previously under treatment for chronic myocardial insufficiency. They had been receiving various diuretics, but ammonium nitrate was the only diuretic used for several days prior to starting the STO tablets. This explains the relatively small weight losses which were recorded in most of the "good" results. Massive edema was infrequent; it occurred only in Cases 1 and 12 (hospital patients) and in Case 36. This was an ambulatory patient who had been discharged from the hospital one month previously and was becoming progressively more dyspneic. These all responded well to the tablets.

TABLE II

CASE NO.	SEX	AGE	RESULTS			INITIAL WT. LOSS			TOTAL DURA- TION	TOTAL NO. TAB.	TOXIC EF- FCTS	DIAGNOSIS
			GOOD	FAIR	NONE	LBS.	DAYS	TAB. USED				
1.	F.	44	*			24	9	34	9 d.	31	0	Hypertension
2.	M.	71	*			12	6	48	8 m.	450	0	Cirrhosis of liver
3.	F.	40	*			5	1	5	16 m.	624	+	Hypertension
4.	M.	73	*			3	3	10	1 m.	80	0	Phlebitis—Legs
5.	F.	74	*	*		--	--	--	14 d.	68	+	Hypertension
6.	M.	67	*			17	20	50	15 m.	481	0	Syphilitic aortitis
7.	F.	51	*			7	8	12	5 w.	33	+	Mitral stenosis
8.	M.	64	*	*		--	--	--	3 m.	110	+	Hypertension
9.	F.	79	*			5	7	8	4 m.	112	0	Hypertension
10.	F.	62	*			4	5	18	2 w.	22	+	Hypertension
11.	M.	72	*			17	9	54	2 m.	98	0	Cor. dis.
12.	F.	42	*			25	8	43	6 w.	102	0	Aortic stenosis
13.	M.	50	*		*	--	--	--	3 d.	15	+	Mitral stenosis
14.	F.	53	*			6	11	30	3 m.	226	-	Cor. dis.
15.	F.	50	*			8	6	54	6 w.	175	-	Mitral stenosis
16.	M.	69	*			3	5	20	8 d.	20	-	Hypertension
17.	F.	59	*			16	14	112	12 m.	550	-	Mitral stenosis
18.	M.	46	*	*		--	--	--	6 w.	155	-	Mitral stenosis
19.	F.	45	*			--	--	--	2 w.	30	-	Hypertension
20.	M.	48	*			10	5	15	3 w.	25	-	Cor. dis.
21.	F.	54	*			Marked diuresis		30	6 w.	55	*	Cor. dis.
22.	F.	70	*		*	--	--	--	2 w.	21	-	Hypertension
23.	M.	80	*			8	14	35	9 w.	100	-	Hypertension
24.	F.	60	*			Marked diuresis		--	1 d.	6	-	Cor. dis.
25.	M.	56	*			3	1	5	1 d.	5	-	Cor. dis.
26.	M.	44	*			10	7	10	1 m.	25	*	Aortic stenosis
27.	M.	50	*		*	--	--	--	1 w.	10	-	Cirrhosis
28.	F.	60	*		*	--	--	--	1 d.	5	-	Ca. ovary
29.	M.	56	*			5	5	15	1 w.	15	-	Cor. dis.
30.	F.	75	*			Marked diuresis		--	3 w.	13	*	Ca. rectum
31.	M.	61	*		*	--	--	--	2 w.	20	*	Cor. dis.
32.	F.	53	*			7	5	8	1 w.	8	-	Mitral stenosis
33.	F.	53	*			10	5	20	22 w.	706	-	Hypertension
34.	M.	63	*			10	4	24	10 m.	250	-	Hypertension
35.	F.	69	*			8	12	48	5 m.	261	*	Hypertension
36.	M.	55	*			28	35	210	2 m.	282	-	Mitral stenosis
37.	M.	62	*			4	2	12	5 m.	98	*	Cirrhosis
38.	F.	64	*			--	--	--	4 d.	4	-	Hypertension
39.	M.	49	*		*	--	--	--	7 d.	42	-	Mitral stenosis
Total			29	4	6						14	

Age.—The patients ranged in age from forty to eighty years. There were eight between forty and fifty years, twelve between fifty and sixty years, eleven between sixty and seventy years, and eight between seventy and eighty years. This is shown in Table II, which gives the distribution of results and toxicity among the various age groups. The number is too small to be of value in drawing conclusions, but it appears that age plays no part in the results, and that no unusual risk is involved in giving the drug to elderly patients.

Sex.—Taking the edematous patients as they presented themselves, twenty women and nineteen men were given the tablets. As shown in Table II, there was no significant difference in the responses of the two sexes. The difference in toxic manifestations was not significant.

Dosage.—The first fifteen patients received a single dose, as has been the custom with the intravenous route. Usually this was five tablets, which is a total of 0.1584 Gm. of mercury, or approximately twice the amount (0.0792 Gm.) in the usual 2 c.c. intravenous dose of salyrgan theophylline. Of these patients, seven developed toxic symptoms, and six had no diuresis. It was then decided to give the tablets in varying and divided doses, in an attempt to learn the effective dose for each patient. One tablet was given after meals, and the dose was increased to the point of effective diuresis or the appearance of toxic effects. Satisfactory results rarely occurred with less than six tablets daily, and this was adopted as a safe starting dose. Occasionally as many as nine tablets daily were necessary for diuresis. Larger doses produced toxic effects.

Patients now have been given the tablets as long as sixteen months without objective or subjective evidence of toxicity. The total number of tablets taken varied greatly, as shown in Table II. Thirteen patients received a total of more than 100 tablets. In only one of them, Case 35, did toxic effects necessitate cessation of medication. There was no indication that prolonged administration was harmful; seventeen patients have used the tablets over a period of six weeks to twenty months.

Mode of Action.—When the drug was given in a fairly large single dose (as is done with the intravenous method), a successful result was marked by the appearance of diuresis in six to eight hours, persisting for about six hours. Some increase in urinary output persisted for twenty-four hours, and, occasionally, the effect lasted into the second day, but not longer. Patients who had been uncomfortable with such rapid diuresis from intravenous administration experienced the same discomfort when the tablets were given in a quantity sufficient to produce a comparable diuresis. However, many of this group of patients were able to take the tablets in divided daily doses without trouble. In these cases, the diuresis was much milder, appeared in twelve to twenty-four hours, and persisted while the tablets were being given and as long as any edema remained.

Diagnosis.—Table I shows the distribution of the patients, the therapeutic results, and the incidence of toxic effect, according to clinical diagnosis. There were twenty-two patients with degenerative heart disease (coronary sclerosis and hypertension), ten with rheumatic heart disease, three with hepatic cirrhosis, one with syphilitic aortitis, and one each with thrombophlebitis of the legs, carcinoma of the ovary with metastasis, and carcinoma of the rectum. (When multiple diagnoses were made, the predominating factor was used in this table.) From the table it appears that no particular etiologic group yielded a better clinical response to the STO tablets than other groups. However, a proportionally greater number of toxic effects occurred in the degenerative heart disease groups.

Results.—Table II shows that twenty-eight patients had good results from the STO tablets. It is of interest that ten of these are listed under "Toxic Effects." However, in only two of these was it necessary to discontinue medication, for the toxic effects were transitory. One of these was Case 30, a woman, aged seventy-four, who had carcinoma of the rectum, with severe nutritional anemia, associated with dyspnea. She was much improved by profuse diuresis, but severe abdominal colic made it inadvisable to continue the use of the drug. The other patient, Case 35, a woman, aged sixty-nine, was able early to take the tablets with less weakness and abdominal pain than when the intravenous route was used. Later the tablets were not well tolerated, and they were discontinued.

The "fair" results must be regarded as satisfactory, for in those cases it was possible to dispense with intravenous administration after initial diuresis, which was the object desired.

Of the thirty-nine patients, the diuresis was unsatisfactory in only six. A brief résumé of these follows:

CASE 13.—Male, aged forty-two, with mitral stenosis and marked edema and ascites, had responded well to mercurial diuretics intravenously. He failed to have diuresis on five STO tablets daily for three days, after which they had to be discontinued on account of nausea and abdominal distress.

CASE 22.—Female, aged seventy, with hypertensive heart disease, was one of the early cases, and only three tablets every other day were given. No results were obtained over a period of three weeks; the medication was stopped, and the patient was not seen again.

CASE 23.—Male, aged fifty, with hepatic cirrhosis, was given two doses of five tablets, four days apart, with no effect.

CASE 28.—Female, aged sixty-six, with carcinoma of the ovary and ascites, was given only one dose of five tablets; no response was obtained.

CASE 31.—Male, aged sixty-one, with coronary sclerosis, was given three tablets daily to supplement weekly injections of 2 c.c. of salyrgan-theophylline. Patient continued to gain weight, and the drug had to be stopped because of toxicity.

CASE 39.—Male, aged forty-nine, with mitral stenosis. No diuresis was obtained after two weeks; the patient received six tablets daily.

Only one of these failures (Case 31) was definitely the result of intolerance to the drug. Others might have been, but the trials were unsatisfactory because none were given further treatment after a rest, and none had received the maximum number of tablets which were often necessary to produce diuresis.

Toxic Effects.—No evidence of kidney irritation or blood disturbance was found. Nausea, vomiting, diarrhea, abdominal discomfort and pain, and general weakness were the toxic effects which were noted. In general, these were not severe. One or more occurred in fourteen patients. In half of these the effects were transitory, and the medication continued. In four the tablets were not given again because the patients remained free of edema. In three cases the use of STO tablets was

discontinued because of recurring abdominal discomfort and diarrhea on repeated trials. A brief discussion of the symptoms and their significance follows:

Nausea occurred seven times. In three patients it was mild, occurred only with the early doses, and further medication was continued. In four patients the medication was stopped. Two of these patients were unable to resume it, and two were not given a further trial. Nausea was twice associated with vomiting, once in each case, and was a minor incident.

Diarrhea occurred six times. In Case 3, in which the patient is still under treatment, it occurs about once a week. The tablets are then stopped for twenty-four hours, the diarrhea ceases, and the medication is resumed. In Case 7 the patient had three loose defecations after each dose of three tablets, given every two days; medication was not interrupted. In Case 26 the patient had several loose movements after single doses of five tablets; the medication was continued. In Case 30 the patient had many loose movements, associated with pain, on taking one tablet twice daily. Medication was stopped. In Case 31 the patient had two to four watery movements, associated with marked abdominal distress, after two tablets daily; medication was discontinued. In Case 35 the patient had two watery stools after a dose of two tablets. Marked discomfort made it necessary to stop medication.

Abdominal pain, in the form of colicky, cramp-like discomfort, occurred in three cases. In Case 21 the patient received eleven doses of five tablets each over a period of six weeks; she had severe pain with the first dose, but none thereafter. In Case 30 the patient had severe pains after each dose of two or three tablets, and had to discontinue them. In Case 5 the patient had marked pain after the first two doses of three each, but none subsequently. The pain is distinguished from abdominal discomfort by its severity and acuteness. Discomfort is not uncommon when one asks about it, but only four patients volunteered the complaint. It was not sufficient to indicate stopping the tablets.

Many patients who are receiving effective doses of mercurial diuretics intravenously complain of marked general weakness for about twenty-four hours after the administration. This has also occurred three times in this series. In Case 3 it was quite marked after five-tablet doses, and did not occur when divided daily doses of three to six tablets were given. In Case 35 the patient complained of weakness regardless of the mode of administration. In Case 37 the patient had this symptom with early doses, but gradually overcame the tendency.

In general, it may be said that the toxic effects were usually not severe, that they were often transitory, and that they showed no tendency to affect vital functions. In most instances they did not prevent further effective use of the tablets. Diarrhea is the most likely of all the toxic symptoms to make it impossible to use the drug.

DISCUSSION

At this stage of the study it appears that two STO tablets three times a day is the best method of starting the drug, and is a dose which will be tolerated well generally. With this dosage one may expect enough diuresis to cause a weight loss of one to eight pounds daily; the effect is most pronounced in those patients who have the greatest amount of edema, and diminishes as the edema becomes less. When the edema has disappeared and no further weight loss occurs, the dose of STO tablets was reduced to an amount necessary to prevent reaccumulation of fluid. Frequently it has been possible, after a period of time, meanwhile keeping the patient's activities within the limits permitted by his cardiac reserve, to discontinue the tablets without recurrence of the edema. In these cases it was occasionally necessary to continue the ammonium nitrate, but not always. In Cases 6 and 8 it was possible to discontinue the STO tablets for several weeks at a time before recurring edema, associated with overexertion, necessitated resumption of the treatment. It can be stated definitely that divided daily doses, varying in size according to the need for diuresis, and maintained at a level sufficient to prevent the accumulation of edema, constitute the most satisfactory method of using the tablets.

The variable response of some patients to intravenous administration also occurs with oral administration. In Case 2 the patient failed to show diuresis on six tablets daily for three weeks, but, after an interval of four months, good diuresis was obtained, with a weight loss of fourteen pounds; his status was maintained without STO tablets after they had been stopped two months later. In Case 23 the patient, on five tablets every other day, had no diuresis for one month, then lost ten pounds in two weeks. Thereafter his weight remained constant, and he showed marked clinical improvement without the mercurial. In Case 34 the patient, who has been under observation for ten months, has shown marked variability in his response. Over a period of several weeks no results were obtained from the STO, either in reducing the edema or maintaining freedom from edema. Sometimes the tablets would maintain a given weight after it had been reduced by intravenous administration, whereas, at others, a very satisfactory diuresis was effected by the STO tablets. On the whole the results in this case were considered satisfactory.

SUMMARY

Salyrgan-theophylline, in the form of enteric-coated tablets for oral administration, was used as a diuretic in thirty-nine patients.

Satisfactory diuresis occurred in twenty-nine patients.

Toxic effects were noted in fourteen patients, usually in the form of irritation of the colon, but these were seldom severe.

Experiences in ascertaining the ideal dosage are described, and a method of using the tablets is suggested.

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Clinical Reports

SUDDEN DEATH OF A RUGBY INTERNATIONAL AFTER A TEST GAME

E. H. CLUVER, M.D.,* AND E. JOKI, M.D.†
JOHANNESBURG, SOUTH AFRICA

CASE REPORT

AFTER having played a strenuous game at Johannesburg in July, 1940, S. C. J., 32 years of age, captain of the Transvaal Representative Rugby Team, collapsed and died.

Autopsy.—The body was that of an adult, European male, and was well built and muscular. Weight was 169 pounds; height, 6 feet. There was marked cyanosis of the face, neck, shoulders, and fingernails. No gross abnormalities of the central nervous system were detected. There were congestion of the vessels of the brain and marked engorgement of the veins on the surface.

Significant pathologic changes were found in the circulatory system. The heart was generally hypertrophied, and weighed 482 Gm. (17 ounces). The hypertrophy was most apparent in the left ventricle, the wall of which measured 2.7 cm. in thickness. There was dilatation of all of the cavities of the heart, especially of the right ventricle, which also showed hypertrophy. Its wall was 0.7 cm. thick. The papillary muscles were markedly thickened and prominent. Macroscopically, the myocardium appeared firm. However, numerous fibrotic patches were irregularly distributed in the left ventricle. The aortic valve was competent, although the cusps were slightly thickened. The mitral valve, which was also competent, admitted two fingers. On the surface of the mitral valve there was a large atheromatous patch.

The left coronary artery showed numerous atheromatous areas which had caused marked narrowing of the lumen at three places. One of these atheromatous areas was located at the orifice of the left coronary artery, and another at a point about midway along the anterior descending branch. Atheromatous patches were also present in the right coronary artery. The diameter of the ascending aorta and the aortic arch was normal, but the wall was extraordinarily soft and thin. The descending aorta measured a little over half an inch in diameter, which is less than half the normal size. There were many atheromatous patches in various parts of the intima.

There was congestion of the thoracic and abdominal organs. The trachea and bronchi contained thick mucus. The lungs were slightly emphysematous and showed some edema and a slight excess of pigmentation. The hilar nodes were considerably enlarged.

The liver was congested, but otherwise normal; it weighed 2,495 Gm. (5½ pounds). There was considerable congestion of the spleen, and it was enlarged (weight, 454 Gm.); on section it showed a marked excess of lymphoid tissue.

Received for publication Sept. 26, 1940.

*Director, South African Institute for Medical Research.

†Head of Department of Physical Education, Witwatersrand Technical College, Johannesburg, South Africa.

The left kidney was very small (weight, 62 Gm.), and was the seat of advanced hydronephrosis. The parenchyma was stretched and thinned, and the pelvis was much dilated. The left ureter was sharply kinked about one inch above the bladder. The right kidney was greatly hypertrophied (weight, 330 Gm.).

There was a persistent thymus gland which weighed 26 Gm. (normal weight at this age, 15 Gm., according to Wolf¹ and Cowdry²). The genital organs were conspicuously small.

Microscopic Examination.—There were several areas of fibrosis in the heart muscle. The papillary muscles and the base of the left ventricle were especially affected. Areas of narrowing of the coronary arteries showed marked atheromatous thickening. The intima was greatly distorted. Atheromatous changes were also found in the aorta. The thymus gland contained scattered foci of entirely normal thymus tissue embedded in fatty tissue; there were areas of considerable infiltration and several large collections of lymphocytes. Numerous Hassall's corpuscles of large size were observed. The blood supply of the gland was abundant. The entire picture was that of an active gland, rather than the involutionary structure which one would expect at the age of 32 years (Aschoff³). Sections of the left kidney revealed normal tissue, although there was extreme congestion. The right kidney showed chronic pyelitis, fibrous thickening of the capsule, patchy fibrosis, and infiltration of the parenchyma with small round cells. All lymphoid structures were hyperplastic, including those of the throat, nasopharynx, intestinal canal, and the lymph nodes.

Previous History.—L. had been one of the most prominent South African rugby players of the preceding decade. He was known as "the iron man of rugby." He had represented his country on the playing fields of South Africa, Britain, Australia, and New Zealand. His identical twin brother J. also died during exertion at the age of 30 years. J. was bathing in the water at the coast when he suddenly collapsed and was swept away. The following information was kindly supplied by Major Danie Craven, captain of the Springbok team:

"I have known L. since 1931, and played on the same team with him on numerous occasions. During 1937 and 1938, I traveled with him to Australia and New Zealand, and roomed with him at various places. I always regarded L. as a very ill man. He used to complain of severe pain in the lower portion of his back. This pain he thought was due to kidney trouble. On many occasions I had to massage his back because of these pains. He also suffered from boils. After every football match he felt sick. He used to put his finger into his throat until he vomited, after which he felt better. He could not take any alcoholic drinks because they also made him sick. His stamina was exceptionally good. However, in the course of the Australia-New Zealand tour, two years prior to his death, his efficiency deteriorated greatly. During the last matches of the tour his performance was very poor. His strength was outstanding, and on the boat he performed wrestling matches with the strongest of his teammates. He always had a husky voice, and suffered from chronic bronchitis. When he was tired, as, for example, after a game, he breathed heavily and noisily. He smoked at least thirty cigarettes a day.

"His twin brother J., whom I also knew very well, was apparently an identical twin. J. looked the same as L., had the same husky voice, and played the same type of game as his brother. In 1937, J. went swimming at Port Elizabeth inside the fenced portion of the beach. It was a quiet day and the water looked like a lake. After a few minutes of bathing, J. suddenly collapsed and sank. His body was never found."

Very little information is available concerning L.'s condition immediately prior to his death. It could be ascertained, however, that, between February and July, 1940, he lost more than 20 pounds in weight. This may have indicated failing health. A roentgenogram of his chest which was taken a few months before he

died (anteroposterior; distance, 5 feet; standing) does not show as much cardiac hypertrophy as was present at autopsy. Unfortunately, no lateral roentgenogram was made.

DISCUSSION

This is a case in which a congenital developmental abnormality caused a fatal circulatory crisis in a first-class athlete. There are many remarkable features. First of all, the deceased's twin brother had died two years before, also during exertion. Unfortunately, post-mortem examination in this instance was not possible; otherwise it is more than likely that an attempt could have been made to prevent the second catastrophe. Second, study of this case emphasizes the truth of the statement made on previous occasions^{4, 5} that even an extraordinarily high standard of physical efficiency is not at all a reliable indicator of the state of health of the athlete concerned. The outstanding performances of L. were possible in spite of a grossly abnormal circulatory system.

The probable development of the disease and mechanism of death may be as follows:

Development of Disease.—Persistence of the thymus gland arrested the normal puberty and postpuberty development of the circulatory system. This arrest of growth, which also affected the urogenital system, caused the descending aorta to remain in an infantile state. Consequently, the heart was compelled to pump against a greatly increased resistance. It may be assumed that the arterial blood pressure was high. Hypertrophy and dilatation of the heart followed. The lymphatic tissue throughout the body was more active than usual and the spleen was greatly enlarged.

The early development of atheromatosis can be interpreted as a result of the extraordinary hydrodynamic strain upon blood vessel walls, a strain which, under the pathologic circumstances, was aggravated by strenuous physical activities.

The heart had to work under most unfavorable conditions, and the multiple fibrotic patches in the myocardium bear witness to the deficiencies of blood supply. It is remarkable that, with such a circulatory system, the man had been capable of such outstanding physical performances. As similar observations have been communicated by one of us (Jokl^{4, 6}) on several previous occasions, it may now be accepted as an established fact that there is no strict relationship between heart disease and even an outstandingly high exercise tolerance.

Mechanism of Death.—The mechanism of death in this case seems clear. The deceased had taken part in a strenuous game. The oxygen requirements of his heart were thus greatly increased. After the game he took a hot bath. This must have shifted large amounts of blood from the intestinal circulation into the skin. In combination with the physiologic fall of blood pressure after the exercise, this must have added to the existing deficiency of blood supply to the coronary artery. The

significance of such physiologic phases in the causation of the final collapse of a diseased circulation has recently been demonstrated by Blumgart, Schlesinger, and Davis.⁷ Furthermore, we have evidence that there were accumulation and stasis of inflammatory exudate in the hydro-nephrotic right kidney, which caused contractions of the smooth muscle of the renal pelvis and ureter. It is probable that unphysiologic tension in intestinal cavities elicits, by means of a reflex, spastic contraction of the coronary arteries. This has been proved conclusively for the stomach.⁸ The autopsy also revealed signs of infection of the respiratory tract. This must have caused a further impairment of the functional efficiency of the heart.

In 1844, Rokitansky⁹ drew attention to the simultaneous occurrence in adults of an infantile aorta, hypertrophy of the heart, and underdevelopment of the genital system. Although it has been assumed for a long time that the thymus gland exerts a direct influence on puberty and postpuberty development, it is only now that a more detailed picture can be drawn. We are especially indebted to Timme,¹⁰ whose studies made possible a full understanding of the condition known as status thymicolymphaticus. Timme showed that the effects of persistence of the thymus gland, leading to arrest of development, mostly at puberty, are often compensated by hyperfunction of other glands in the body. The primary abnormalities caused by thymic persistence are lymphoid hyperplasia, gonadal and adrenal deficiency, a low blood sugar level, low blood pressure, and hypoplasia of the heart and vessels. In most cases, marked compensatory efforts of the organism lead after some time to a profound change in the picture.

The suprarenal cortex and the pituitary are strongly stimulated. We have asked ourselves whether the high standard of physical efficiency of this rugby player could perhaps be explained partly by a special compensatory effort of the suprarenal cortex. The changes in the heart were clearly the result of an attempt on the part of the circulatory system to overcome the obstacle created by the underdevelopment of the descending aorta.

Wolf¹ states that one of the three possible causes of death in cases of status thymicolymphaticus is weakness of the muscular coat of the arteries which renders them incapable of withstanding sudden changes in blood pressure. This would apply in our case.

In view of the circumstances under which the sudden death of L. and his twin brother occurred, Wolf's suggestion that swimming and bathing should be forbidden to people suffering from status thymicolymphaticus appears to be well founded.

SUMMARY

Summarizing, it appears that death occurred because of sudden coronary insufficiency. There was narrowing of the coronary artery

caused by atheromatosis. There was the physiologic fall of blood pressure after the exercise. Large amounts of blood were shifted into the skin as a result of taking a hot bath. The oxygen requirements of the heart muscle were greatly increased after the exercise. It is probable that reflex spasm of the coronary artery was caused by the frustrated efforts of the diseased right kidney to expel its inflammatory contents. It may be assumed that permeability of the myocardial cell membranes was adversely affected by the concurrent infection of the respiratory system.

This observation allows a detailed analysis of a case of status thymico-lymphaticus, a term which has in the past often been used in a rather general way. We can trace the history of the patient back to the persistence of the thymus gland after puberty. We can thus understand the arresting effect of this primary developmental disturbance upon the maturation of the descending aorta. This latter anatomic deficiency explains the secondary pathologic reactions which created the above described extraordinary situation and caused death.

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TEMPORAL ARTERITIS

C. L. SCHAEFER, M.D., AND C. E. SANDERS, M.D.
KANSAS CITY, KAN.

TEMPORAL arteritis, an unusual and new syndrome, was first described by Horton, Magath, and Brown,¹ in 1934. Since that time, only a few similar cases have been reported. A patient with this disease who was treated on the Sanders oscillating bed is reported in this paper.

CASE REPORT

A white woman, aged 62 years, was first seen at her home because of excruciating pain in the right temporal region, fever, sweats, dizziness, gastric distress, and general malaise. Approximately three weeks previously, the patient complained of a mild unilateral headache which could not be relieved with the ordinary sedatives. This was soon followed by fever, sweats, and general malaise. During the preceding week, dizziness, gastric distress, and vomiting were added to the list of complaints. Her past history was essentially negative. Because of the grave condition of the patient and the severity of her symptoms, she was admitted to the hospital.

Physical examination revealed a swelling which extended upward for approximately 2½ inches from the right temporomandibular joint. The surrounding skin was moderately hyperemic. The right temporal artery was very prominent, tortuous, thickened, and tender. There were no palpable nodules. Pulsations were absent in the right temporal artery, but present in the left. There was a rather marked hyperesthesia of the entire right side of the scalp. The pupils were contracted and equal. The pupils were dilated with a mydriatic and the eyes examined on several occasions by Dr. Morris Simpson. A slight opacity of the right lens was found, but the vessels were normal and there was no evidence of choking of the discs. The ears, nose, and throat appeared normal. No lymph node enlargement was found. The lungs and heart were essentially negative. The blood pressure was 155/80. No organs could be palpated on abdominal examination. The reflexes were slightly hyperactive. The temperature ranged from 99° to 101° F. The pulse rate varied from 98 to 124.

The hemoglobin was 89 per cent, the erythrocyte count, 4,630,000, and the leucocyte count, 9,750. The differential leucocyte count showed 91 per cent polymorphonuclear cells (filamented, 81 per cent, nonfilamented, 10 per cent) and 9 per cent lymphocytes. The color index was 0.9. The blood Wassermann reaction was negative. There was no nitrogen retention in the blood, and the blood culture was negative. The urine was normal. The spinal fluid was clear and colorless. It gave positive Pandy and Ross-Jones tests, and the colloidal gold curve was 4444444321. The spinal fluid Wassermann reaction was negative. There was no pleocytosis.

The patient's condition became progressively worse. The headache was unbearable and could not be controlled with ½ gr. of morphine intramuscularly. She appeared desperately ill, did not respond very well, and her speech became slurred. Finally, the patient became delirious, and the possibility of brain tumor with increased intracranial pressure was considered. Dr. Frank Teachnor was called in

consultation. However, the neurologic examination was essentially negative, except for a suggestively positive Babinski and Chaddock on the left. On later and repeated examinations, the Babinski and Chaddock were found to be definitely negative. Roentgenologic examination of the head revealed increased vascular markings in the left frontal area, limited to the inner table, high in the vertical plane of the left frontal area. There was no evidence of tumor or increased intracranial tension. The sella turcica appeared normal.

On entering the hospital, the patient received 50 c.c. of a 50 per cent glucose solution intravenously, $\frac{1}{2}$ gr. of morphine intramuscularly, an ice cap to the head, and a 1-2-3 enema; the head of the bed was elevated. However, the patient did not obtain any appreciable relief until 2 gr. of sodium luminal were given intramuscularly. On awakening, the symptoms were as severe as ever. Cibulgin tablets were given by mouth without results. Finally, the patient was put on the Sanders oscillating bed, and enjoyed her first symptomless and natural sleep without any medication. She showed remarkable improvement on the bed and was dismissed from the hospital in ten days. The patient remained on the bed at home for the next six weeks, oscillating the bed twenty-four hours a day for the first four weeks, and approximately fifteen hours a day for the last two weeks. She made a remarkable recovery, appears alert, and is entirely free from symptoms. The swelling above the right temporomandibular joint receded, and the surrounding skin is normal in appearance. Although pulsations have returned, the right temporal artery is still a little thickened. Up to January 2, 1941, none of the old symptoms have returned. The final diagnosis of temporal arteritis was made entirely from the clinical manifestations. The close resemblance of this localized condition to that in other cases which have been reported justifies the above diagnosis.

COMMENT

Little is known of this new type of localized arteritis, and the etiology and pathologic criteria are not as yet established. In the cases which have been reported, the only relief from symptoms was obtained by resection of the involved portion of the temporal vessel. Since the oscillating bed has been used with such success in the treatment of peripheral vascular diseases, we felt justified in trying it for this new peripheral vascular syndrome. The result exceeded our expectations.

SUMMARY

A case of temporal arteritis is reported. The patient was successfully treated on the Sanders oscillating bed.

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THE ELECTROCARDIOGRAM IN TRAUMATIC PERICARDITIS

CASE REPORT

R. LANGENDORF, M.D., AND S. GOLDBERG, M.D.
CHICAGO, ILL.

THE value of electrocardiographic changes after injury of the heart by stab or gunshot wounds of the chest has been definitely established.¹⁻⁵ Previously the alterations of the S-T segment and T wave were ascribed either to direct damage to the myocardium, or to coronary artery injury, or to ligation of a coronary vessel, with subsequent infarction of the myocardium. The diffuse pericarditis which is invariably present in cases of injury of the heart may explain the discrepancy between the electrocardiographic pattern and that of myocardial infarction alone. Diffuse pericarditis has a distinct electrocardiographic pattern of its own.^{4, 6-10}

The following report of a pericardial stab wound is presented because it clearly demonstrates the role which diffuse pericarditis plays in causing electrocardiographic abnormalities. In this case there was neither gross myocardial involvement nor any coronary vessel damage. This was demonstrated during the operation which was undertaken to stop hemorrhage from the lacerated pericardium, lung, and chest wall.

CASE REPORT

M. J., a 30-year-old colored woman, was brought into the emergency room of Michael Reese Hospital on the night of Oct. 15, 1939. She had sustained a stab wound of the left anterior chest wall about 5 inches long, centered below the nipple, and extending upward and outward toward the axilla. The wound was bleeding profusely. A quarter of a grain of morphine was given hypodermically, and an intravenous infusion of physiologic saline solution was begun. Consciousness was at a low enough ebb to permit exploration of the wound without giving her an anesthetic. The entire chest wall had been opened, with complete transection of the fifth rib. Several bleeding vessels were clamped and the wound was spread, exposing the lung and pericardium. There was bleeding from a laceration in the lung about an inch long. This was quickly controlled by sutures. There was a tear in the pericardium near the base of the heart about an inch in length, with venous bleeding that was controlled by several ligatures. The myocardium was found to be uninjured, and there was little free blood in the pericardial sac. The pericardium was loosely sutured to prevent pleurocardial adhesions. Several hundred cubic centimeters of blood were left in the pleural cavity, and the chest wall was quickly closed with interrupted catgut sutures in the muscle and fascia, and silk in the skin. The closure was airtight.

From the Cardiovascular and Surgical Depts., Michael Reese Hospital.
Aided by the A. D. Nast Fund for Cardiac Research.
Received for publication Jan. 4, 1941.

The blood pressure was now only 80/60 mm. Hg. The pulse rate was 120, and the quality of the pulse was poor. Respiration was increased, but not embarrassed. The patient was given neacina solution and human serum intravenously, and two hours later the blood pressure was 130/98, the pulse rate, 96, and the patient had regained consciousness.

The next morning her general condition remained fairly good. The right border of the heart was percussed 2 cm. to the right of the sternum. The entire left hemithorax was dull, and the breath sounds were suppressed over the upper lobe and absent over the lower. The erythrocyte count was 2,800,000 and the hemoglobin, 40 per cent.

Improvement was gradual until October 20. Dyspnea occurred occasionally and was always relieved by morphine. Roentgenograms of the chest confirmed the diagnosis of massive hydropneumothorax. At no time were there any clinical signs of cardiac tamponade. A pericardial friction rub was first heard October 20. On October 21 thoracentesis was performed because of the severe dyspnea, and 450 c.c. of blood were removed, leaving a positive pleural pressure. After this procedure, the pulse rate fell from 140 to 120 and the respirations from 38 to 30 per minute, and there was considerable subjective improvement.

On October 23 the temperature rose to 102.6° F. rectally, and the pericardial friction rub was more pronounced. Because of recurrent respiratory distress, the patient was placed in an oxygen tent and improved greatly. Oxygen therapy was discontinued October 26. Thereafter improvement was gradual, though slow. The wound healing was primary, and the sutures were removed on the thirteenth day. The only complication was abdominal distress and vomiting on several occasions; this was controlled by a dry diet. The lung re-expanded slowly; roentgenograms showed about 50 per cent collapse on November 1. On November 21 the patient was sent to a convalescent home. On December 13 a roentgenogram showed complete aeration of the upper lobe and only a barely recognizable amount of fluid in the lower part of the chest. The temperature remained normal after November 7.

COMMENT

This patient's electrocardiograms (Fig. 1) showed the changes which are expected in diffuse pericarditis. No significant QRS changes occurred. There was a concordant elevation of the S-T segment in the limb leads on October 23, and this was replaced by T inversion in all the limb leads on November 6 which waned and eventually disappeared. At the same time QRS was entirely up in Lead CF_2 ; inversion of the T waves appeared in the chest leads on November 6, and waned and disappeared in subsequent records. These mutations and the time of their evolution are not characteristic of myocardial infarction, but are typical of diffuse pericarditis of other than traumatic origin.

The electrocardiograms in this case failed to show any of the characteristic QRS changes in any of the leads or the discordant deviation of the S-T segment and the T wave in Leads I and III which occurs in the usual case of recent myocardial infarction. A local area of myocardial necrosis of traumatic origin would be expected to produce one of the classical patterns of recent myocardial infarction, provided it was properly located. This occurs because patients who have traumatic necrosis

rarely have any preceding cardiac disease. Therefore, the absence of a characteristic coronary contour may be taken as evidence against the presence of massive necrosis of the myocardium. Obviously, if diffuse pericarditis complicates massive necrosis of the myocardium, a composite electrocardiographic pattern may be expected.

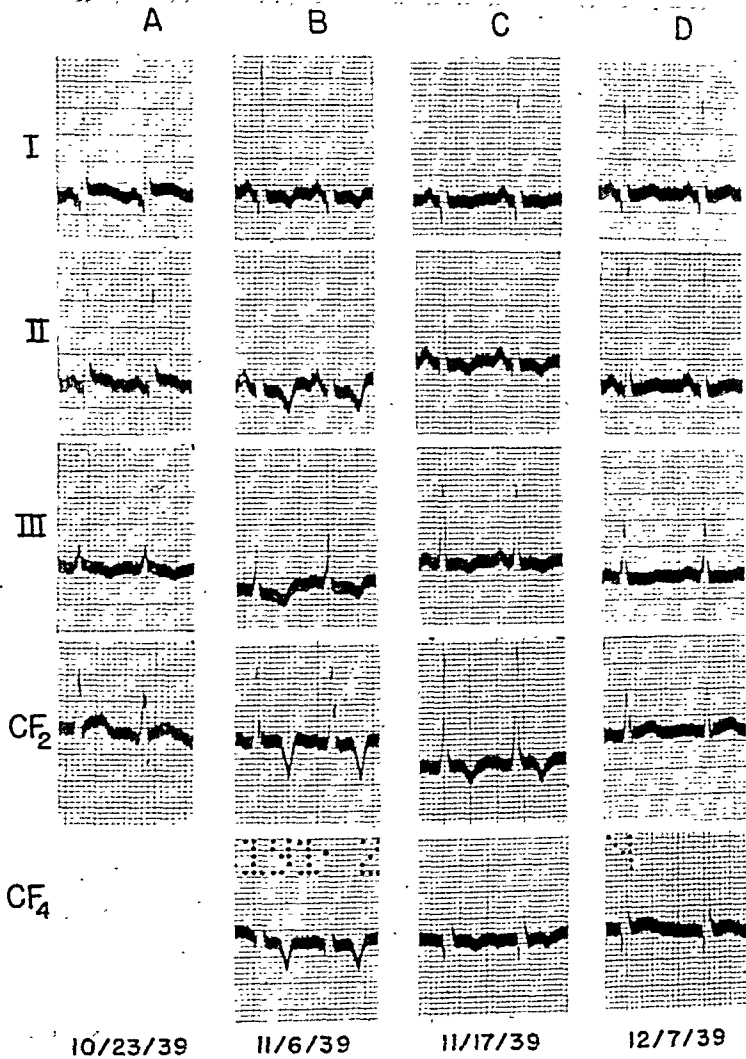


Fig. 1.

A correct interpretation of the mechanism which is responsible for the electrocardiographic changes is important in considering the prognosis in cases of traumatic heart involvement. This may also become important from a medicolegal standpoint. Histologic examination of the heart in cases of diffuse pericarditis has shown that the inflammatory process is confined to the uppermost layers of the myocardium.^{11, 12} Because of this, the amount of myocardial damage is much more restricted than would be the case if the myocardium had been traumatized or the coronary circulation interfered with. Although myocarditis secondary to diffuse pericarditis may lower the functional capacity of the heart, it

does so to a lesser extent than localized massive necrosis of the heart muscle. Recognition of the peculiar type of electrocardiographic change which diffuse pericarditis can produce helps to distinguish this condition from myocardial infarction.

This case, which is unique as far as we can ascertain, presented the opportunity to make a complete electrocardiographic study of traumatic diffuse pericarditis, unassociated with myocardial damage other than that which the pericarditis itself causes in the subepicardial layers. It therefore helps to establish clearly the peculiar contour which diffuse pericarditis produces in the electrocardiogram, and lends experimental support to the view that there is a particular electrocardiographic pattern in diffuse pericarditis. In this human experiment there was no complicating factor which could disturb the electrocardiographic picture, although the temporary pericardial effusion and the acute hemorrhage and shock may have altered the abnormalities in the first record. However, the steady evolution of the electrocardiographic changes over a period of six weeks makes it unlikely that these factors played any considerable role. The evidence seems clear from the examination at the time of operation that the myocardium and the coronary vessels were not affected.

This experience raises a question as to the extent to which diffuse pericarditis in other cases of stab and gunshot wounds of the chest was responsible for some of the electrocardiographic alterations that have been reported.

SUMMARY

A case of stab wound of the chest is reported, in which, at operation, which was done to stop bleeding, only a laceration of the parietal pericardium (and lungs) occurred, without trauma to the epicardium, myocardium, or coronary blood vessels. The opportunity of following the electrocardiographic changes in serial records was afforded. The clinical course and electrocardiographic pattern were those of traumatic diffuse pericarditis. A distinction is made between such electrocardiographic changes and those which occur after localized myocardial necrosis of traumatic origin.

We are grateful to Dr. L. N. Katz for his help in preparing this report.

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UNUSUAL SITE OF AN ANEURYSM OF THE AORTA

WILLIAM DRESSLER, M.D.
NEW YORK, N. Y.

ANEURYSMS originate most frequently from the ascending part of the aorta, and have a tendency to develop toward the right side. Distention and displacement of the aortic wall in this direction are favored by the minimum resistance offered by the lung, as well as by the fact that the right wall of the ascending aorta receives the greatest impact from the column of blood which is expelled during systole; for the outflow tract of the left ventricle runs an oblique course from low on the left to high on the right. Aortic aneurysms which arise from the ascending aorta and extend toward the left side of the chest are exceedingly rare, and create unusual clinical pictures which may cause considerable diagnostic difficulties.

CASE REPORT*

A 52-year-old white man had acquired syphilis at the age of 23. He had never had antisyphilitic treatment, except local applications. The Wassermann reaction was said to have been invariably negative. There were no other diseases.

Eight years earlier the patient started to have shortness of breath during severe effort, such as mountain climbing. Thereafter his condition remained unchanged for seven and one-half years, after which time a definite deterioration began to take place. Shortness of breath became more intense and occurred even on slight effort. A severe pressing and burning pain was simultaneously experienced in the precordium, with radiation to the back and down the left arm to the fingertips. Attacks of nocturnal dyspnea occurred several times, and were associated with rattling in the chest and expectoration of white, frothy sputum. During the preceding six months the patient had lost more than 16 pounds in weight. Recently the attacks of precordial pain had become more frequent and occurred even when the patient was at rest. He also complained of a persistent feeling of soreness in the precordial area. In November, 1931, he was admitted to the hospital.

The patient was of gracile body build and moderately well nourished. His face showed a slightly livid discoloration. There was no edema or ascites. A loud stridor was audible even when the patient was at rest. The slightest effort in bed caused marked dyspnea. No distinct pulsations were observed in the veins of the neck, and there were no dilated cutaneous veins on the chest. There was no difference in temperature, skin color, or pulse between the two halves of the body. The pupils were circular, equal in size, and reacted promptly to light and in accommodation. There was no tracheal tug.

Received for publication Feb. 1, 1941.

*The case was demonstrated by Dr. Stefan Feher at a meeting of the Society of Internal Medicine, in Vienna.

The percussion note was hyperresonant over the right lung. The left half of the diaphragm was at the level of the tenth rib, and did not descend with deep inspiration. The right half of the diaphragm was about 4 cm. below this level, and underwent normal inspiratory movement. Normal vesicular breathing was heard over the right lung, whereas breath sounds were barely audible over the left side.

The precordial region was prominent, and the skin over the precordium was edematous. The precordial bulge extended upward to the third and downward to the sixth rib; it extended from the left border of the sternum to the fourth intercostal space, 3 cm. beyond the left midclavicular line. The points of greatest convexity of the bulge, at the fourth and fifth ribs, were tender to palpation. There was a distinct pulsatory heaving of the prominent area during systole; this was most pronounced in the fourth intercostal space at the left mid-clavicular line (Fig. 1). The lower end of the sternum also showed a slight pulsation. No circumscribed apex beat was visible or palpable.

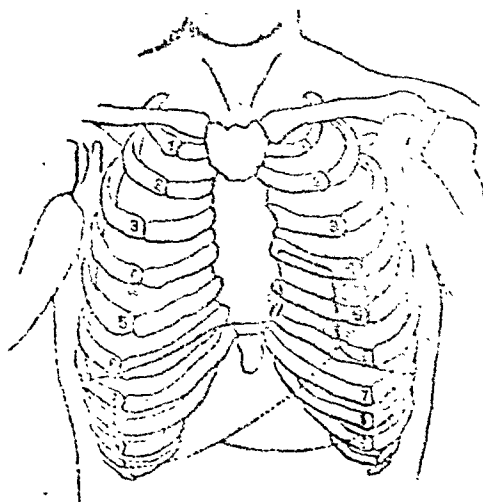


Fig. 1.—The area of pulsatory heaving is indicated by shading. The pulsation was most striking at the level of the fourth intercostal space in the left mid-clavicular line; it extended cranially to the third and caudally to the sixth rib, and reached the sternum medially.

Percussion revealed marked dullness over the sternum below the attachment of the third costal cartilage. Distinct dullness for a distance of about 3 cm. was also observed in the fifth right intercostal space adjacent to the sternum. On the left side there was no abnormal dullness in the second intercostal space, but marked dullness was found in the third intercostal space, covering an area of about 6 cm. In the fourth and fifth left intercostal spaces there was flatness which extended from the sternum to the left midclavicular line.

On auscultation, feeble heart sounds and a faint systolic murmur were heard over the point of maximum prominence in the fourth intercostal space. The second heart sound was louder than the first. In the second right intercostal space an accentuated second sound and a short, rather loud, systolic murmur were audible, in addition to a soft bruit of whistling character. The musical murmur was transmitted to the lower end of the sternum and second left intercostal space. It was not influenced by posture or respiration. No thrills were palpable over the chest. The pulsation in the carotid and radial arteries was feeble, but there was no pulse difference in the symmetrical arteries. The wall of the radial artery was soft, and the blood pressure 100/80 mm. Hg.

The abdomen was not distended. The liver extended about 3 cm. below the costal arch in the right mid-clavicular line; the spleen was not palpable. The urine was normal except for an increase in the amount of urobilinogen. The Wassermann reaction was positive. The electrocardiogram showed right axis deviation and normal sinus rhythm.

The roentgenologic abnormalities were unusual (only an orthodiagram was available, Fig. 2). The cardiac silhouette was bizarre, especially at the left border, where an irregular, approximately pear-shaped mass, with sharp outlines, seemed to be adherent. The contour of the left ventricle could not be differentiated from this abnormal shadow. The aorta appeared slightly dilated; its arch and descending portion could be readily differentiated from the abnormal mass at the left of the silhouette. The trachea showed marked deviation to the right. The radiologist thought that the abnormal shadow was caused by a mass adjacent to the heart at the left, and suggested the possibility of an encapsulated pericardial effusion. However, aneurysm of the aorta could not be excluded, although it seemed less likely because of the site of this abnormal shadow.

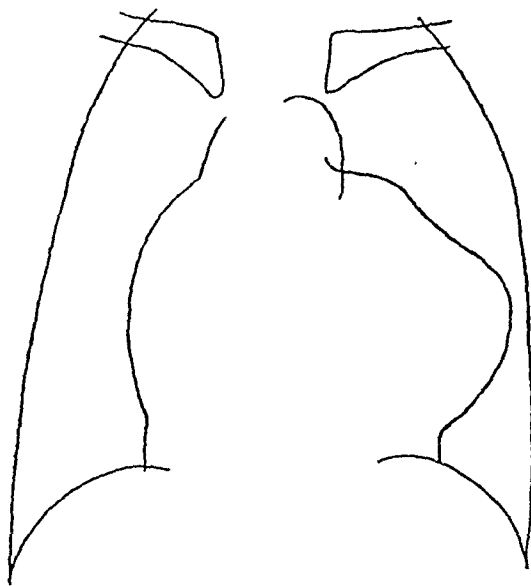


Fig. 2.—Orthodiagram, showing enlargement of the cardiovascular silhouette to the left, with a bizarre shape of the left border.

The history and clinical observations did not lend support to the assumption of encapsulated pericardial effusion. The broad pulsation in the precordial area aroused suspicion of a cardiac aneurysm,¹ to which the anginal attacks could also be attributed. However, the electrocardiogram did not support this opinion. The bizarre bulge at the left side of the roentgenologic silhouette started at the attachment of the second costal cartilage, i.e., at a higher level than is usual for a cardiac aneurysm. Also, there were symptoms pointing to erosion of ribs, which is not known to be caused by cardiac aneurysm. The same is true for bronchostenosis, which was distinctly manifest in our case. All the symptoms and signs that we had observed could be accounted for by an aneurysm of a large vessel, and this diagnosis was supported by the history of syphilis. The localization at the left of the sternum drew our attention to the pulmonary artery. However, aneurysms of the pulmonary artery are usually characterized by pulsations in the second intercostal space²; dilatations large enough to cause a pulsation in the third and fourth intercostal

spaces have not, as far as we know, been reported. Hence, aneurysm of the aorta, with unusual localization, seemed the most likely pathologic condition. Since on roentgenologic examination the arch and descending part of the aorta could be differentiated from the abnormal shadow, it seemed most probable that the aneurysm was of the ascending aorta, and that it had extended toward the left and displaced the heart.

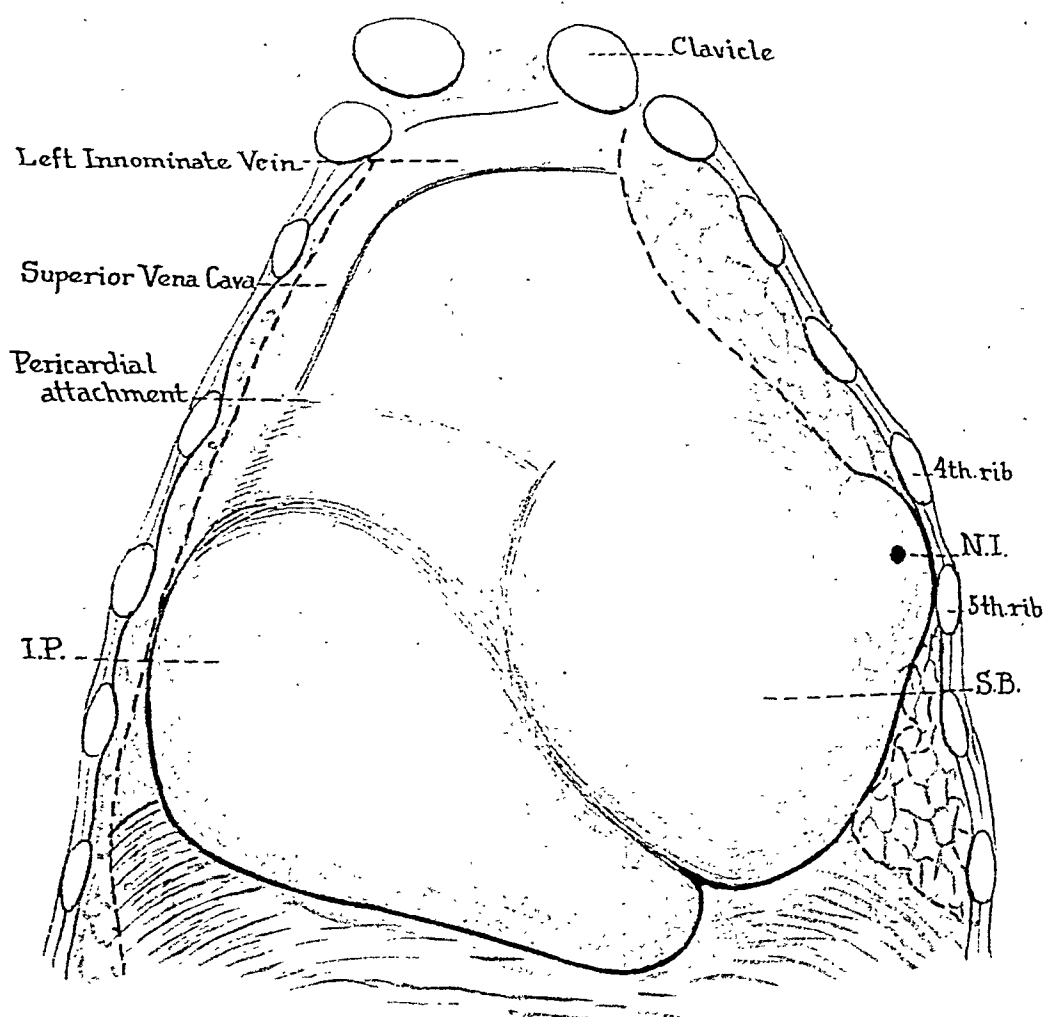


Fig. 3.—The anterior mediastinum after removal of the greater part of the anterior thoracic wall. The lungs are forced laterally and dorsad by the enlarged mediastinum. A large, semispherical bulge is visible on the left side, protruding against the fourth and fifth ribs. A needle that was inserted into the chest vertically at the area of an irregular, dark-blue prominence is visible, extending up to a horizontal line (attachment of the pericardium) running about 2 cm. above the bulge. *I.P.*, Irregular prominence; *N.I.*, point of needle insertion; *S.B.*, semispherical bulge.

The patient's condition improved after a few days' rest in bed; the sensation of soreness in the precordium diminished and the dyspnea was less distressing. The patient insisted on leaving the hospital, and died suddenly a few days later.

Necropsy revealed marked enlargement of the anterior mediastinum (Fig. 3), which forced the lungs on either side laterad and dorsally. The mediastinum displayed two prominences. One, at the left, was semispherical, and protruded between the fourth and fifth ribs. It was separated by a furrow from an irregular bulge that made up the lower part of the right half of the mediastinum. Here there was a blue,

translucent discoloration up to a horizontal line which ran about 2 cm. above the irregular bulge. At the right and cranially the dark translucent band of the superior vena cava and left innominate veins was visible.

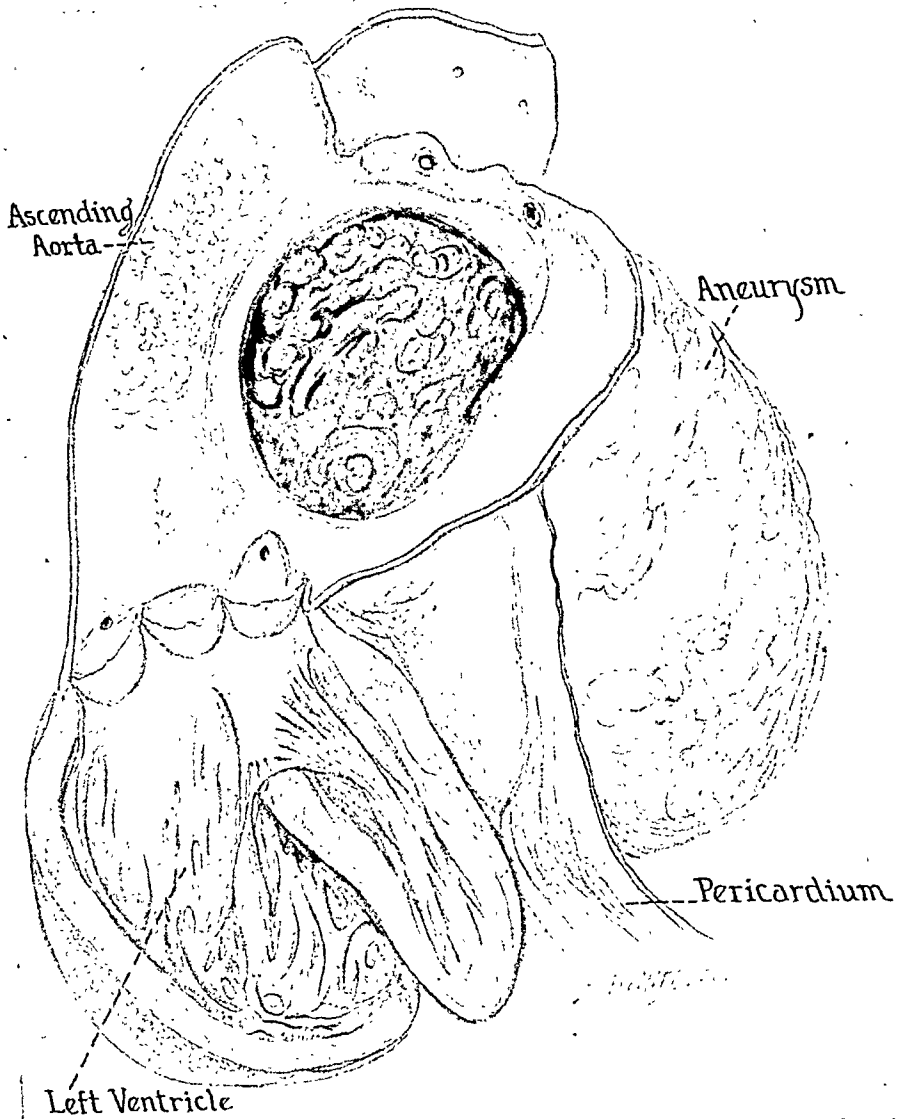


Fig. 4.—The left ventricle and the ascending part of the aorta have been opened. A large, round opening in the left wall of the aorta leads into an aneurysmal sac larger than a man's fist. The other portions of the aortic wall display remarkably little change. The left coronary orifice is pulled upward by the traction of the aneurysm. Note the close relationship of the aneurysm to the left coronary artery. The medial portion of the aneurysm is covered by the pericardium; the heart is displaced to the right.

The left semispherical prominence, which corresponded to the bulge observed clinically in the precordium, and seemed to be caused by the pericardium, was opened first. It contained a large amount of blood clots around a large, centrally located thrombus. The irregular bulge at the right side was formed by the heart and pericardium (Fig. 4). The pericardial sac was filled with a large quantity of blood, partly fluid and partly clotted; this was responsible for the translucent, blue discoloration. The heart was of normal size, its walls were not hypertrophied,

and the valves were intact. The intima of the ascending aorta showed slight scarring caused by syphilitic aortitis. At the left border of the aorta there was a circular opening, measuring 7 cm. in diameter, which led into an aneurysmal sac. The aneurysm was larger than a man's fist; it was filled with blood clots enclosing a large thrombus (as described above). This aneurysm had produced the semispherical bulge at the left half of the mediastinum. Expanding to the left and caudad, it had displaced the heart to the right and forced its left margin dorsad, thus causing a rotation of the heart from right to left (as seen from the front). The aneurysm was partly covered by the pericardium. A small perforation, just large enough to admit a thick probe, and leading into the pericardial cavity, was discovered at the lower border of the aneurysmal sac. The coronary orifices were of normal size. The left coronary ostium was displaced cranially by the traction of the aneurysm.

COMMENT

Extraordinary anatomic conditions, which occur only exceptionally, were responsible in our case for the unusual situation of the aortic aneurysm. There was remarkably little involvement of the wall of the aorta by syphilitic infiltration and destruction, except for a sharply limited circular area at the left border. This region was gradually stretched and distended, and the resulting aneurysm had expanded to the left and caudad, displacing the heart and causing it to rotate from right to left. This rotation produced a deviation of the electrical axis to the right in the electrocardiogram. Other sequelae of the aneurysm were compression of the left bronchus, resulting in dyspnea, diminished breath sounds over the left lung, and stridulous breathing; the anginal pains were caused by syphilitic inflammation of the aortic wall and pressure of the aneurysm on neighboring structures. The explanation of the attacks of pulmonary edema is more difficult, for such common causes as hypertension and aortic valve lesions were absent. There was no extension of the syphilitic infiltration to the valves of the aorta. However, the close topographic relationship of the aneurysmal tumor to the left coronary artery and to the heart suggests that pressure on the coronary artery and possibly on the left ventricle was responsible for left-sided heart failure and attacks of pulmonary edema.

SUMMARY

A case of syphilitic aortitis is presented, with almost exclusive involvement of the left side of the ascending aorta. A huge aneurysm developed to the left and extended caudad to the precordial region. It displaced the heart to the right and caused a rotation of the heart from right to left; this resulted in right axis deviation in the electrocardiogram. The aneurysm produced a broad pulsation and eroded several ribs in the precordial area between the third and sixth ribs.

REFERENCES

1. Dressler, W., and Pfeiffer, R.: Cardiac Aneurysm, A Report of Ten Cases, *Ann. Int. Med.* 14: 100, 1940.
2. Henschen, S. E.: Das Aneurysma der Arteria pulmonalis, *Samml. klin. Vortr. von Volkmann*. N.F. No. 422-423, *Inn. Med.* p. 126, 1906.

Abstracts and Reviews

Selected Abstracts

Fishback, D. B., Guttman, S. A., and Abramson, E. B.: An Objective Method of Determining Blood Velocity (Fluorescein Method). *Am. J. M. Sc.* 203: 535, 1942.

A new objective circulation time test has been described, using fluorescein.

The data obtained indicate that the method is reasonably simple, not harmful to the patient, and reliable as indicated by comparison with other methods.

This method is of particular advantage in determining the blood velocity in small children, comatose, anesthetized, mentally ill, and moribund patients.

In patients with normal hearts or fully compensated cardiac disease, the circulation time varied from seven to 15.6 seconds. In another group of patients with cardiac disease undergoing decompensation, the circulation time varied from sixteen to twenty-five seconds, one being forty-five seconds.

AUTHORS.

Mahaim, E., and Winston, M. R.: Researches on the Comparative Anatomy and the Experimental Pathology of the Superior Connections of Bundle His-Tawara. *Cardiologia* 5: 189, 1941.

The His-Tawara bundle is not completely isolated from the musculature of the ventricular septum. There exist delicate connections which unite it to the upper part of the ventricular septum.

These upper connections are always to be found in man and the following animals: sheep, calf, dog, cat, rabbit. They are dispersed, varying in their caliber and topography. They are mostly direct; sometimes indirect and sometimes instantaneous. It is possible to identify them only in an uninterrupted series of slides.

These upper connections are of functional importance in physiopathology. They explain the lack of auriculo-ventricular block when both branches are destroyed simultaneously (*bloc bilatéral manqué*). The experimentation confirms the existence of this para-specific septal conduction.

In physiopathology these upper connections assume the functions of a substitutional organ. They explain the contradictions which occur in the anatomoclinical researches on bundle branch block.

In the normal cardiac contraction these upper connections probably assure a direct conduction between the specific tissue and the musculature of the upper part of the ventricular septum, in a region which does not directly communicate with Purkinje's terminal network.

AUTHORS.

Mackby, M. J.: *Cephalic Bruit. A Review of the Literature and a Report of Six Cases.* *Am. J. Surg.* 55: 534, 1942.

It appears that cranial auscultation is a "near forgotten art." This method of examination is seldom employed by the average practitioner although simple of execution, and from such an examination one may derive valuable information. The pertinent features of the subject as recorded in the literature have been reviewed. Six examples of intracranial bruit occurring in patients harboring intracranial lesions have been reported in order to illustrate some of the pathologic states that may result in a bruit. In an endeavor to estimate the frequency of occurrence of this abnormal physical finding in persons not exhibiting signs of intracranial disturbances, the heads of 250 persons were auscultated. Cephalic bruit was demonstrated in only three instances (0.012 per cent) and in two of these cases, there was a murmur audible over the heart, the great vessels of the neck and the head. From evidence at hand, it seems logical to conclude that a cephalic bruit in any individual merits careful consideration and further investigation of the possible presence of an organic intracranial lesion.

AUTHOR.

Gregg, D. E., Shipley, R. E., Eckstein, R. W., Rotta, A., and Wearn, J. T.: *Measurement of Mean Blood Flow in Arteries and Veins by Means of the Rotameter.* *Proc. Soc. Exper. Biol. & Med.* 49: 267-72, 1942.

The rotameter has been used to measure cardiac input and mean blood flow in the arteries and veins of the anesthetized dog. Typical records are shown. Tests indicate that in routine use the instrument will give reliable blood flow values with an error of less than 10 per cent. Its use enables the experimenter to determine at a glance the moment-to-moment flow during the time that flow is actually being measured, an advantage not possessed by any other known method. The rotameter is so simple in operation that it should also serve a very useful purpose for the measurement of blood flows in student experiments in the classroom for which as yet no simple and reliable method has been available.

AUTHORS.

Berghoff, R. S., Geraci, A. S., and Hirsch, D. A.: *Senile Ectasy: A Clinical Study of the Aging Human Heart (Observations on Four Hundred Patients).* *Illinois M. J.* 81: 97, 1942.

This is a preliminary report of an investigation of four hundred of a total of one thousand cardiacs in the age group of fifty to eighty years. The material gathered consumed five and one-half years and embodies case histories, physical examinations, percussion measurements checked by telefluoroscopies and electrocardiograms. This incomplete study led to the following conclusions:

The most common forms of heart disease encountered in senescence are arteriosclerotic, hypertensive, syphilitic, rheumatic, and thyroid. The earliest subjective symptoms are dyspnea, heart consciousness, and pain. The outstanding and most important diagnostic physical sign is altered configuration of the heart. Percussion carefully carried out is reliable and has greater diagnostic value than auscultation. Telefluoroscopy is a simple, economical and practical diagnostic adjunct to percussion. The electrocardiograph furnishes more help in this age group than in any other types of heart disease. It is possible and practical to differentiate clinically three different stages of coronary disease. A fair working knowledge concerning the immediate prognosis of the various individual types of heart disease encountered in senile individuals has been presented.

AUTHORS.

Robb, J. S., and Robb, R. C.: Hypertension Electrocardiograms Experimentally Produced and Anatomically Explained. I. Cor Pulmonale. *Am. J. M. Sc.* 203: 625, 1942.

Electrocardiograms taken in experimental right heart failure agree in form with those of previous authors.

Whatever the cause, pulmonary hypertension, if immediately great, may produce acute right heart dilatation, or if sufficiently prolonged, results in right heart hypertrophy and eventually in failure.

The essential mechanism of failure consists in the progressive stretching of the three component muscles of the right ventricle. The weakest area at the right apex is formed by the superficial sinospiral muscle and strain of this muscle is heralded by some elevation of RS-T in all leads. A second weak area, the superficial bulbospiral portion of the apex, becomes involved and this is recognized by further elevation of RS-T in Leads II and III and coincident depression of S-T in Lead I. Widening at the base indicates failure of the deep sinospiral and is evidenced by marked depression of RS-T in Leads II and III, and either elevation or depression of RS-T in Lead I, depending on the degree of concomitant superficial bulbospiral involvement.

It is immaterial whether the exciting cause of muscle failure is rise of pressure within the right heart or whether failure is secondary to asphyxia produced either directly or reflexly. When these muscles are under tension and unduly stretched, the same electrocardiographic picture is produced as if the muscle were infarcted or otherwise damaged.

Because these muscles fail consecutively and because damage to each has its own effect on the electrocardiogram, and especially because there may have been pre-existing disease (or effects due to drug action), a valid explanation is available for the great variation in clinical electrocardiograms during an attack of cor pulmonale.

In these experiments, with the chest open, a dilated right heart was not associated with right axis deviation.

The McGinn-White type of electrocardiogram is probably associated with a moderately severe degree of rise and intracardiac pressure, stretching all three of the component muscles. When intracardiac pressure is dangerously increased, all S-T intervals are depressed in addition to some one or all of the changes described by McGinn and White, or Rösler.

If intracardiac pressure increases slowly, and not too greatly, the electrocardiogram may be wholly unaffected, or if the pressure increases are rapid and extreme, any combination of muscle injury pictures may occur, thus accounting for the variable reports concerning electrocardiograms in pulmonary embolism and hypertension.

The employment of muscle bundle localization may serve to increase the value of electrocardiograms in the recognition, treatment, and prognosis of cor pulmonale.

AUTHORS.

Carrillo, E. G.: Bifid R Wave in Derivation II. With a Note on the Electrocardiogram in Pituitary Basophilism. *Rev. argent. de cardiol.* 8: 401, 1942.

A case of pituitary basophilism (Cushing's syndrome) is described. The patient showed signs of myocardial weakness and died of a cerebral hemorrhage. In the electrocardiogram a bifid R wave in Lead II was observed. The pathologic significance of this electrocardiographic abnormality is insisted upon.

AUTHOR.

Robb, J. S., and Robb, R. G.: Hypertension Electrocardiograms Experimentally Produced and Anatomically Explained. II. Left Ventricular Strain. *Am. J. M. Sc.* 203: 634, 1942.

Because in acute experiments on young animals no hypertrophy and myocardial damage (in the sense of infarct or connective tissue replacement) is present, one must attribute the various results to change in size of the ventricles dependent upon "strain," that is increased intraventricular pressure with dilatation (rather than hypertrophy).

Such a stretching of the musculature demonstrably alters conduction even to the point of causing ventricular fibrillation.

Either development of an injury current within a single muscle band or differential slowing of conduction (including recovery) may be regarded as the essential factor resulting in the characteristic electrocardiograms.

These S-T shifts in the electrocardiogram, caused by putting strain upon the individual muscle bundles, are the same as those produced by experimental infarction of the same muscle bundles.

Acute centralized systemic hypertension, experimentally induced, initiates a series of electrocardiographic changes reflecting the severity of the disturbance. The left ventricle is enclosed by four muscle masses which give way in sequence: the superficial sinospiral first, the superficial bulbospiral next, later the deep sinospiral muscle, and in extremis, the deep bulbospiral muscle. The authors' clinical experience parallels the animal data.

AUTHORS.

Morelli, A. C.: Diagnostic Tomography of Stenosis of the Isthmus of the Aorta and of Persistence of the Arterial Canal. *Rev. argent. de cardiol.* 8: 371, 1942.

The author modifies his method of extrarapid tomography in order to study the posterior mediastinus. He uses short exposures (0.1 sec.), medium voltage, high amperage, small fields, antidifusor and horizontal dispersion. With this technique he has been able to visualize an aortic coarctation showing all its pathological characteristics. A comparative study was made with a case of angulation of the aorta. In two cases of persistence of the ductus arteriosus, the ductus was seen as a shadow uniting the aortic knob with the left branch of the pulmonary artery. This shadow has also been seen in apparently normal persons, that had, however, a dilatation of the pulmonary artery. It is suggested that these latter cases correspond to those in which there is a persistence of the ductus arteriosus without continuous murmur, as observed by Abbott in one-fifth of her cases.

AUTHOR.

Weisman, S. J.: Congenital Idiopathic Cardiac Hypertrophy. *Arch. Path.* 33: 365, 1942.

Congenital idiopathic cardiac hypertrophy is enlargement of the heart by hypertrophy and dilation, associated frequently with thickening of the endocardium. The true cases, according to Kugel and Stoloff, show no myocardial changes, although perivascular fibrosis has been described frequently by others. No other lesion or anomaly is present in the true cases. Too few cases of anomaly of the coronary circulation have been described along with idiopathic hypertrophy to support any causal relation. When such anomaly is present, the resulting changes have not been the same as in true idiopathic hypertrophy. It seems logical to assume that the association of the two defects is accidental. Fetal myocarditis has not yet been proved to be the etiologic factor in the hypertrophy. Although, as knowledge of

abnormal conditions of the infant heart increases, fewer cases of cardiac hypertrophy are considered cases of idiopathic hypertrophy, there still remain many which cannot be explained.

The author reports two cases with findings at autopsy. No mention is made of the part played by glycogen storage dysfunction in this type of heart lesion.

AUTHOR.

Cushing, E. H., Feil, H. S., Stanton, E. J., and Wartman, W. B.: Infarction of the Cardiac Auricles (Atria): Clinical, Pathological, and Experimental Studies. Brit. Heart J. 4: 17, 1942.

Infarction of the cardiac auricles (atria) was found in 17 per cent of 182 cases of myocardial infarction that were proved at autopsy. Abnormalities in the auricular complex of the electrocardiogram were present in 74 per cent of the cases of atrial infarction, but in only 9 per cent of all cases of infarction of the ventricles. Ligation of the atrial arteries in dogs produced abnormal auricular mechanism in only 6 out of 20 experiments. In 4 additional experiments there was a transient change in the contour of the P wave. Depression of the P-Q segment of the electrocardiogram was seen in 4 instances in which the atrial arteries were ligated. Abnormality in auricular mechanism is the most reliable clue to the clinical diagnosis of infarction of the atria.

AUTHORS.

Console, A. D.: Relation of Cardiac Lesions to the Clinical Course of Rheumatic Fever. Arch. Int. Med. 69: 551, 1942.

Of 98 cases in which endocarditis or pericarditis, found at autopsy, had been preceded by a history of rheumatic fever with polyarthritis or other similar manifestations of disease, Aschoff bodies were found in all in which death occurred during the first decade of life, in 64 per cent of those in which it occurred during the second decade and in 11 per cent of those in which it occurred during a later decade.

When Aschoff bodies were found in the myocardium (28 cases) with 1 exception the interval between the last attack of polyarthritis and death was five months or less.

In 3 cases in which Aschoff bodies occurred in the myocardium there was no history of polyarthritis, chorea or other clinical evidence of acute rheumatic infection.

A curve of the frequency of death in cases in which the symptoms of rheumatic fever and cardiac lesions occurred at different age periods shows two distinct peaks, one in the first decades of life, corresponding with deaths from cardiac failure and the presence of Aschoff bodies in the myocardium, and the other between the ages of 40 and 60 years, associated with cardiac failure, deforming lesions of the valves and an absence of Aschoff bodies.

Minor degrees of valvular deformity preponderated in the first three decades of life, whereas advanced deformity was common in the later decades. Valvular deformity increased with the duration of the disease after the onset of symptoms but had no constant relation to the number of attacks or to the age at onset.

AUTHOR.

Mainzer, F., and Krause, M.: The Electrocardiogram in the Bronchial Asthma Paroxysm. Cardiologia 5: 261, 1941.

In 8 out of 16 patients with bronchial asthma the electrocardiographic tracings were found to be altered during the asthmatic paroxysm. The deformations present were: a low ventricular complex, notching within the ventricular complex

and particularly deformation of S-T and T. Moreover, as a rule, there was also tachycardia (120 a minute). Neither the electrocardiographic changes nor tachycardia disappeared, at least in some cases, until a lapse of several days after the attack.

Changes in the position of the heart can be excluded from bringing out the electrocardiographic phenomena; the alterations are considered to be due to myocardial anoxemia. The anoxemia is deemed to be brought about by insufficient O_2 -saturation of the arterial blood as well as a reduced coronary circulation through hemodynamic disturbances or nervous stimuli (increased arterial pressure in the pulmonary circulation, increased vagal tone); tachycardia may also be active on these lines.

Sometimes neither the tachycardia nor the changes of the electrocardiographic curve disappeared until after some considerable time. From this fact (which we have not had the opportunity of studying in detail) we may conclude that the cardiac lesion produced by the asthmatic attack cannot be considered as being merely mechanical in nature. It is highly probable that the asthmatic paroxysm leaves the same marks upon the myocardium as other transitory anoxemic conditions do (angina pectoris attack, CO poisoning, muscular exertion in anemic persons).

In this way it becomes clear that the chronic circulatory disturbance developing during the course of bronchial asthma may be explained as well by the effect of recurring attacks of anoxemia on the myocardium as by mechanical overstrain imposed on the pulmonary circulation.

AUTHORS.

McPhedran, H.: Cardiovascular Changes in Toxic Goiter. *Canad. M. A. J.* 46: 471, 1942.

Reviews the cardiovascular changes found in connection with toxic goiter. From 1934 to 1940 inclusive, there have been treated in our wards at St. Michael's Hospital 115 cases diagnosed as toxic goiter and operated upon as such. A careful analysis of these cases from the cardiovascular standpoint has been made, and the result of this survey is herewith presented.

Of the total of 116 cases, 56 cases were found to present abnormal cardiovascular findings.

In this latter group, 19, or 33.9 per cent, were found at or below 40, and 37, or 66.1 per cent, above 40 years of age, with the largest group of all between 50 and 60 years. There were 16 males and 40 females.

AUTHOR.

Shelburne, S., Hawley, J. L., and McGee, A. S.: Retinal Arteriovenous Nicking: Relation to Enlargement of the Heart in Ambulatory Patients With Hypertension. *Arch. Int. Med.* 69: 213, 1941.

The authors were able to show by their study of 317 patients with hypertension that retinal arteriovenous nicking is so closely related to enlargement of the heart that if this lesion is found one may expect to find an enlarged heart. Furthermore, if this lesion is found in a patient with enlargement of the heart, the latter condition can be accounted for by hypertension, even if the blood pressure is normal at the time of examination. It may also be stated that if the heart of a hypertensive patient is enlarged and no arteriovenous nicking is found, the enlargement is not likely to be due to hypertension alone and a careful search for other lesions, such as those of severe coronary arterial disease, syphilis or rheumatic fever, is clearly indicated.

There is apparently no relation between the early change in the retinal arteries, which the authors have designated early arteriovenous nicking, and enlargement of the heart, but the later change, which they have called moderate arteriovenous nicking, is definitely related to enlargement of the heart, though not so closely as the fully developed lesion (definite arteriovenous nicking).

Arteriovenous nicking is important in the differentiation of the chronic nephritis associated with late hypertension and chronic glomerulonephritis.

It is hoped that this study will help to show the importance of careful observation of the changes in the retinal vessels and the necessity for more accurate description. There are too many reports, even from the best institutions, in which retinal arteriosclerosis is evaluated as 4 plus or grade 3 but the lesions are not described. Such a notation is meaningless. It is much more valuable to state whether arteriovenous nicking, extremely narrow arteries, changes in the caliber in arteries, etc., are present.

AUTHORS.

Ray, B. S.: Cerebral Arteriovenous Aneurysms. Surg., Gynec. & Obst. 73: 615, 1941.

Observations on six patients having cerebral arteriovenous aneurysms substantiate the conclusion that these lesions are congenital and can be identified by the clinical signs and symptoms they produce and by their appearance when exposed at the operating table.

A bruit heard on auscultation over some part of the head, the eyeballs, and the carotid arteries in the neck, is a characteristic sign. This, in conjunction with Jacksonian convulsions or unilateral motor and sensory disturbances, is usually sufficient to permit a diagnosis to be made.

Changes in the skull that may be shown on roentgenogram include slight signs of increased intracranial pressure, increased vascularity of the skull, deepening of the grooves for the middle meningeal arteries, local atrophy of the inner table from direct pressure of the vessels of the aneurysm, enlargement of the head, and calcification in the lesion.

Air studies may be relied upon, in many instances, to demonstrate abnormalities in the ventricles and subarachnoid spaces. Encephalography in such cases is safer than ventriculography.

Cerebral angiography is indicated in order to visualize the extent and the location of the lesion.

The collateral circulation is extensive. It involves anastomosis between the external and internal carotid arterial systems, principally through the orbit and through the meninges.

The effects of the aneurysm upon the general cardiovascular system are variable but not necessarily serious.

Headache, localized on the side of the lesion, is usually due to pain arising in the dilated arteries, chiefly in branches of the external carotid artery.

Reasonably safe methods of treatment include exploratory osteoplastic operation and decompression, successive ligation of the carotid arteries in the neck, and roentgenotherapy. None can be relied upon to be curative, but used alone or in combination they may be beneficial.

Ligation of carotid arteries is safer in persons with cerebral arteriovenous aneurysms than in others because of the rich collateral circulation.

Direct operative attack upon the lesions is dangerous but might be indicated in selected cases.

AUTHOR.

Fulton, G. P., and Lutz, B. R.: Smooth Muscle Motor-Units in Small Blood Vessels. *Am. J. Physiol.* 135: 531, 1942.

Stimulation of minute nerves, with a microelectrode, produced spatially limited vascular responses, generally dilatation followed by constriction, in the small blood vessels of the retrolingual membrane of the frog, *Rana pipiens*. The limited responses suggest the concept of smooth muscle motor-units in small blood vessels.

Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M.: Cardiac Output, Blood and Interstitial Fluid Volumes, Total Circulating Serum Protein, and Kidney Function During Cardiac Failure and After Improvement. *J. Clin. Investigation* 21: 229, 1942.

Estimations of cardiac output, volume of blood and interstitial fluid, concentration and total amount of plasma proteins, and of inulin, phenol red and urea clearances were made on six patients with congestive heart failure and again after restoration of compensation by digitalis and diuretics.

Cardiac output and stroke volume increased with improvement in all cases. The mean minute output during failure was 31 per cent less than after improvement. Effective peripheral resistance decreased coincidentally with improvement.

Blood and serum volumes also decreased with recovery, the mean change in blood volume being 1.15 liters or 25 per cent, and in serum volume 0.92 liter or 35 per cent of the volumes during failure. In spite of a marked decrease in the volume of intercellular fluid, the mean value after restoration of compensation was 32 per cent total body weight, or almost 50 per cent above normal.

While the concentration of serum proteins, particularly of the globulin fraction, increased with clinical improvement, the total amount of circulating protein decreased, due almost entirely to a decrease in serum albumin.

Inulin clearance showed no significant change with improvement, while phenol red clearance increased to approximately the same degree as cardiac output.

AUTHORS.

Theis, F. V., and Freeland, M. R.: Thromboangiitis Obliterans. *Surgery* 11: 101, 1942.

The clinical results in the treatment of the biochemical blood changes in acute or active thromboangiitis obliterans with sodium tetrathionate or sodium thiosulfate and of the peripheral circulatory deficiency due to arterial thromboses with pavaex treatment have been most encouraging.

Deficient oxygenation of the arterial blood was usually present during the active stage of the disease. Following treatment for two to six weeks, the increased oxygenation of the arterial blood was accompanied by clinical improvement and in some cases by clinical recovery (five years).

The oxygenation of the arterial blood in the majority of patients with thromboangiitis obliterans which we studied was affected by smoking.

AUTHORS.

Dublin, L. I., and Marks, H. H.: A Note on the Inheritance of Cardiovascular Disease—Results of Life Insurance Investigations. *J. Mt. Sinai Hosp.* 8: 482, 1942.

These several studies point to a definite relationship between parents and offspring with respect to cardiovascular diseases. The clinical studies have generally shown that among patients with any form or symptom of the diseases, there is a high incidence of these diseases or symptoms in the parental history. In the insurance

studies, it has been found that the total mortality of persons with a family history of these conditions has ranged from approximately normal to well above normal, but in every study in which the death rate from chronic cardiovascular diseases was considered, the mortality from them has been above average. In none of the studies was the mortality of these cases low, even though on the basis of the survivorship of the parents to advanced ages, the history was favorable. It is fair to conclude, therefore, that these studies indicate a familial relationship in the cardiovascular diseases.

The nature of this association cannot be brought out with any great exactness from insurance studies, or indeed from most of the material thus far collected on the subject. It is not likely that this association is a matter of direct inheritance of faulty cardiac or vascular structure in most instances, but rather that a number of factors are involved. For example, insurance studies have shown that the mortality from the cardiovascular-renal diseases is appreciably higher among the obese than among persons of slighter build. Since there are strong hereditary factors in body build or structure, the effect of heredity as regards the incidence of cardiovascular disease may be an indirect one.

The mortality from cardiovascular diseases among those with a family record of early deaths from such diseases is, however, not free from the influence of non-hereditary factors which tend to raise the mortality from them. For example, individuals orphaned at a relatively early age, regardless of the cause of death of the parents, are subject to deleterious environmental conditions associated with broken homes. Among children in such families, the frequency of infections leading to early cardiovascular or renal disease is relatively high. Moreover, many of these children must work at an early age and, consequently, often at unskilled or semi-skilled occupations, and among persons in such occupations the mortality from cardiovascular-renal diseases is appreciably above average.

The question may properly be raised whether a familial association with any cardiovascular disease or its symptoms is unfavorable to longevity. For, if such relationship involved no diminution in longevity, this relationship, while of medical interest, would be of no great consequence. This is by no means the case. The presence of these diseases in abnormal frequency in the family history at an early age is often an indication of the existence of those factors which produce early vascular degeneration. This is indicated by the fact that the excess death rate from these diseases among the persons we have studied is not concentrated at the older ages, and at the longer durations of insurance, but is present at every age and apparently is relatively worse for the shorter durations than the longer ones. Consequently, a great proportion of the deaths of these persons with a poor family record of cardiovascular disease occurs at relatively young ages. A family record of this type must, therefore, be considered generally unfavorable to longevity.

AUTHORS.

Flaxman, N.: Clinical Value of Digitalis in Hypertensive Heart Failure. II. With Sinus Tachycardia. *Am. J. M. Sc.* 203: 747, 1942.

The study of 160 cases of hypertensive heart failure with sinus tachycardia is reported.

The cardiac rate is important as a prognostic sign, because the mortality among these patients, with the exception of A-V nodal rhythm, was the highest of all groups of hypertensives.

Exempted were those with isolated failure of the left ventricle where the mortality, due chiefly to coronary thrombosis, was only 11.3 per cent, as compared with the mortality of 37.7 per cent among those with the combined type of ventricular failure.

Congestive heart failure, the factor controllable by digitalis, was responsible for 34 (69 per cent) of the 49 deaths, but all of these were in patients who had the combined type of failure before the treatment was started.

Digitalis was administered to these hypertensive patients with rapid, regular cardiac rhythm not for its action on the rate, but to relieve the symptoms and signs of heart failure, which it did successfully in 70 per cent of the patients.

AUTHOR.

Wilkinson, K. D.: Two Cases of Digitalis Poisoning. *Brit. Heart J.* 4: 1, 1942.

Two cases of digitalis poisoning in patients with sinus rhythm are recorded. Each showed complete auriculoventricular dissociation; coupled beats; and marked abnormalities in the QRS-T complexes.

Recovery was slow and some degree of heart block persisted for twelve days after the digitalis was discontinued. One case showed bundle branch block as well as auriculoventricular block.

AUTHOR.

Kaltreider, N. L., Meneely, G. R., and Allen, J. R.: The Effect of Epinephrine on the Volume of the Blood. *J. Clin. Investigation* 21: 339, 1942.

Measurements were made at rest of the volume of the blood and its components, and variations in the volumes were followed after the subcutaneous injection of 1 c.c. of epinephrine (1:1000). Further observations included measurements of the blood hemoglobin and viscosity, serum proteins, venous and arterial pressures, velocity of the blood and pulse rate. These observations lead to the following conclusions:

In normal individuals, following the administration of epinephrine, there is a prompt and definite decrease in the plasma volume, which persists in most cases for at least 45 minutes. In the majority of cases there is a slight increase in the cell volume. These alterations are associated with an increase in blood hemoglobin and viscosity and serum proteins. Following the administration of the drug, the systolic pressure increased while the diastolic pressure fell slightly.

In the individuals who have polycythemia vera with splenomegaly, epinephrine causes a definite decrease in the plasma volume, a moderate increase in cell volume with little change in the total volume.

After the injection of epinephrine into 2 individuals whose spleens had been removed, there was a decrease in both blood and plasma volumes, accompanied by a slight decrease in the cell volume.

The effects of severe exercise and of epinephrine on the components of the blood volume are similar.

AUTHORS.

Allen, C. R., Stutzman, J. W., Slocum, H. C., and Orth, O. S.: Protection From Cyclopropane-Epinephrine Tachycardia by Various Drugs. *Anesthesiology* 2: 503, 1941.

Procaine, carbon dioxide, quinidine, morphine, ergotamine, F 883 (diethyl-amino-methyl-benzo-dioxane), and yohimbine have been studied for the prevention of cyclopropane-epinephrine tachycardia. These agents are all protective in proper dosages. The effective amounts per kilogram when administered intravenously are: procaine, 16 mg.; quinidine, 15 mg.; ergotamine, $\frac{1}{6}$ mg.; F 883, 2.0 mg.; and yohimbine, 0.2 mg. The morphine dose was 8 mg. per Kg. when given subcutaneously. Twenty to 24 per cent carbon dioxide in the anesthetic mixture also gave protection.

It is believed that procaine, carbon dioxide, and quinidine give protection from cyclopropane-epinephrine tachycardia because of myocardial depression; F 883 and ergotamine, by their sympatholytic action; yohimbine, through its adrenergic action; and morphine, by producing either functional decerebration or myocardial depression.

AUTHORS.

Book Review

A INSUFICIÊNCIA CORONÁRIA: By Dr. Caio Benjamin Dias, Assistente de Clínica Propedeutica Medica da Faculdade de Medicina da U. M. G. Livraria Editora Paulo Bluhm, Belo Horizonte, 1941, 162 pages, 51 illustrations.

This is an up-to-date and well-written review on the concept of coronary insufficiency, and should be of value to readers of Portuguese who wish to acquaint themselves with the modern views on the subject. The monograph begins with a good summary of recent work on the anatomy and physiology of the coronary circulation, takes up the concept of coronary insufficiency, discusses the general electrocardiographic and anatomic changes, causes, and mechanisms, clinical manifestations, and then closes with a study of the electrocardiogram.

In the last chapter the author also gives his personal experience with exercise tests. The exercise consisted in the rapid climbing of 5 steps, 20 times in succession. Electrocardiograms were taken before and after exercise with the standard leads and Lead IV F. For a positive test the author relies on the following criteria: (1) inversion of the T wave in one or more leads, a diphaseic T, or an exaggeration of a previously negative T; (2) depression of the S-T segment in one or more leads of more than 2 mm., especially when accompanied by such changes in the T wave as flattening, inversion, increase in negativity, or a diphaseic T; (3) appearance of transitory intraventricular conduction defects or either auricular or ventricular extrasystoles from several foci. Seventy tests were performed on 60 subjects, 14 of whom were patients with coronary disease. The conclusions of the author corroborate the experience of others.

There are 13 drawings of electrocardiograms and 37 reproductions of electrocardiographic tracings. The majority of the illustrations are good. There is some evidence of careless editing, such as the absence of Fig. 5 and a serious misprint on page 40, where embolism of the coronary arteries is referred to as "pulmonary embolism." The bibliography lists 163 references.

RAFAEL DOMINGUEZ.

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•*Executive Committee.*

American Heart Journal

VOL. 24

OCTOBER, 1942

No. 4

Original Communications

CLINICAL STUDIES ON DIGOXIN, A PURIFIED DIGITALIS GLYCOSIDE

O. ALAN ROSE, M.D., ROBERT C. BATTERMAN, M.D., AND
ARTHUR C. DEGRAFF, M.D.
NEW YORK, N. Y.

THIS report deals with our observations on patients with congestive heart failure who were treated with digoxin, a pure crystalline glycoside. Although considerable work has been published on digoxin,¹ both experimental and clinical, there has been no study large enough to constitute a thorough clinical evaluation. It is not our purpose at this time to compare the various glycosides, or to indicate the relative superiority of any single preparation.

In recent years the availability of the purified digitalis glycosides has brought about renewed interest in digitalis therapy. Study of the glycosides has clearly demonstrated the inaccuracy of the bio-assay method, in that the cat unit potency of these preparations cannot be directly applied to man.² This makes it necessary to ascertain accurately the clinical potency of each of the glycosides in terms of actual weight. However, once this information is obtained, there is no variation in the potency of the sample, and, therefore, no need for repeated assays of different samples of the same preparation.

Digoxin was isolated from *Digitalis lanata* by Smith,³ in 1930. It is a white crystalline substance which, on hydrolysis, yields one molecule of digoxigenin and three molecules of digitoxose. It is related to lanatoside C, but its molecule contains no glucose or acetyl grouping.

SELECTION OF PATIENTS

The study was conducted on hospitalized and ambulatory patients. The hospitalized patients were selected according to the criteria established in previous studies.⁴ In all cases the criteria used in diagnosis were those of the New York Heart Association.⁵ Patients with recent myocardial infarction, or other com-

From the Department of Therapeutics and the Cardiac Clinic, New York University College of Medicine; the Third Medical Division (New York University), Bellevue Hospital; and the Medical Service, Lenox Hill Hospital, New York.

Received for publication Feb. 26, 1942.

plicating conditions, such as bronchopneumonia or glomerulonephritis, were excluded. Congestive heart failure was present to some degree during the period of hospitalization, although it may not have been discernible at the time of digitalization. All patients were cooperative. None were moribund or too ill to be followed adequately after digitalization. No patients were used who had received any digitalis preparation within at least three weeks prior to the beginning of the study.

METHOD

Before digitalization the maximum effect of the usual supportive measures was evaluated in each case. The patient was then digitalized with digoxin* according to one of three plans. Thirty-three patients were digitalized rapidly by a modification of the Eggleston method.⁶ The initial dose varied between 0.75 and 2.0 mg. Thereafter, a dose ranging from 0.5 to 1.0 mg. was given every six hours until minor signs of toxicity were noted. The second plan consisted of administering single daily doses of 0.25 and 1.5 mg. to nine hospitalized and nine ambulatory patients. In both groups, on the hospitalized patients, observations were made daily in an effort to ascertain the minimal dose necessary to initiate a therapeutic effect and produce minor signs of toxicity. At least one electrocardiogram was taken shortly before digitalization, and others were made at frequent intervals, usually daily, thereafter. All patients were weighed daily to aid in evaluating changes in their cardiac status. This was particularly useful in gauging the therapeutic response of patients with normal sinus rhythm. The ambulatory patients were observed at one- or two-week intervals. Electrocardiograms in this group were taken when a significant therapeutic or toxic effect was observed clinically. All patients were observed closely for evidences of improvement, changes in ventricular and pulse rates, and symptoms and signs of toxicity.

In the third plan of study, each of 13 hospitalized patients, eight of whom had chronic auricular fibrillation with a rapid ventricular rate, received a single dose of digoxin intravenously. The dose varied between 1.5 and 2.5 mg. This relatively large dose was administered because our primary object was to study the rapidity of onset of effect. To insure this it was necessary to give a dose which was known to be well within the therapeutic range. No evidence of toxicity was noted when doses in this range were previously administered to seven normal subjects without heart disease. Herrmann⁷ suggests similar doses in the treatment of patients with congestive heart failure. The intravenous preparation was administered so that 0.5 mg. of digoxin was diluted in 10 c.c. of physiologic saline solution. In this group the ventricular rates, pulse rates, arterial pressures, and venous pressures were taken until constant levels had been established. Digoxin was then administered, and the above observations were repeated at frequent intervals for several hours. Electrocardiograms were taken immediately before, and frequently during, the period of observation.

A study of the maintenance dose of digoxin was made in a group of 24 ambulatory patients, of whom 20 had chronic auricular fibrillation and four had normal sinus rhythm. These patients had no symptoms of diminished cardiac reserve or evidence of congestive heart failure when they were adequately maintained on a digitalis preparation. With the exception of those patients who received digoxin for initial digitalization, all patients were under observation for months or years prior to this study, so that their maintenance requirements of digitalis were known. For

*We are indebted to Burroughs Wellcome and Co., Inc., for the generous supply of material, and other aid in connection with this investigation. Digoxin was supplied in 0.25 and 1.0 mg. tablets. The latter were furnished for investigative use only, to facilitate administration of large doses. The parenteral preparation was supplied in ampoules of 0.50 mg. in alcoholic solution. Using the Hatcher-Brody technique for assay, 0.192 mg. of digoxin is equivalent to one cat unit.

maintenance studies, digoxin was administered in doses varying from 0.25 to 1.5 mg. daily. In those cases in which various doses were given, administration was continued for at least five weeks, and usually eight to ten weeks, in order to evaluate properly each daily dose. At each clinic visit the patients were observed for clinical evidence of congestive heart failure, variation in the ventricular rate, and signs of digitalis toxicity. Electrocardiograms were taken when the daily dose of the drug was changed or when toxicity was noted.

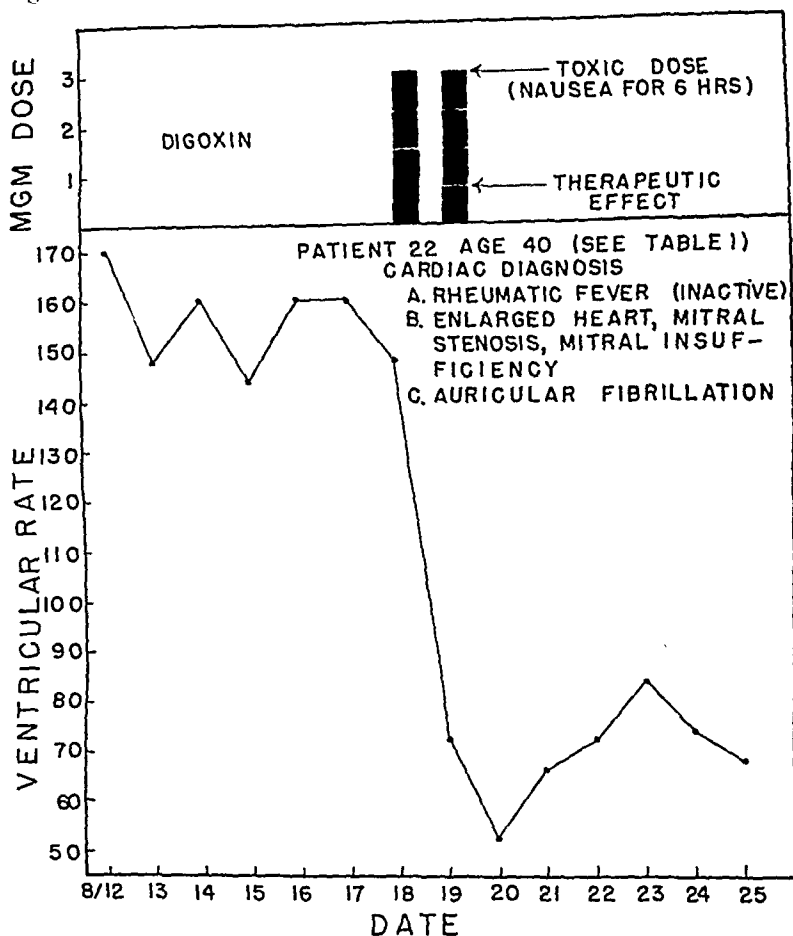


Fig. 1.—Rapid digitalization with digoxin orally in a patient with chronic auricular fibrillation. Therapeutic response noted within 24 hours after administration of 4.5 mg. Toxicity noted after 6.0 mg.

RESULTS

Digoxin was administered by a modification of the Eggleston method to 33 hospitalized patients, of whom 22 had normal sinus rhythm, seven had chronic auricular fibrillation, and four had auricular flutter. The essential data obtained in this group of patients are summarized in Table I. A satisfactory therapeutic response was observed in 23 cases, regardless of the nature of the underlying heart disease, rhythm, or degree of congestive heart failure (Fig. 1). With the exception of Patient 30, this response was noted within twenty-four or forty-eight hours with a dose ranging from 2.0 to 6.0 mg. (average, 3.75 mg.). In

TABLE
THERAPEUTIC AND TOXIC DOSES OF DIG

PA- TIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CON- GESTIVE HEART FAIL- URE*	WEIGHT IN POUNDS
			ETIOLOGIC	ANATOMIC	PHYSIO- LOGIC†		
1	63	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	120
2	53	M	Arteriosclerosis and unknown	Enlarged heart. Aortic stenosis. Aortic insufficiency	NSR	±	166
3	58	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+++	153
4	37	F	Rheumatic fever (inactive). Hypertension	Enlarged heart. Mitral stenosis. Mitral insufficiency	NSR	++	155
5	61	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	N	
6	76	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR Left BBB	++	119
7	55	M	Arteriosclerosis. Pulmonary fibrosis	Enlarged heart. (Cor Pulmonale). Myocardial fibrosis. Coronary sclerosis	NSR	+	128
8	61	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+++	116
9	64	M	Hypertension	Enlarged heart. Dilated aorta	NSR Incomplete left BBB	+	183
10	74	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+++	193
11	38	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+++	193
12	57	M	Hypertension	Enlarged heart	NSR	±	133
13	51	F	Hypertension. Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	++	109

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

†NSR, Normal sinus rhythm; BBB, bundle branch block; AF, auricular fibrillation; VPC, ventricular puncture contraction; VR, ventricular rate.

‡Excluding patient 30.

I

OXIN WITH RAPID DIGITALIZATION ORALLY

DOSE OF DIGOXIN IN MG.		THERAPEUTIC EFFECT	THERAPEUTIC DOSE IN MG.	TOXIC EFFECT	TOXIC DOSE IN MG.	REMARKS
INITIAL DOSE	DOSE EVERY SIX HOURS					
1.0	0.5	Decreased dyspnea	3.0	Nausea and vomiting. Prolonged P-R interval (0.22 second)	5.0	
1.5	1.0			Nausea and vomiting. Prolonged P-R interval (0.23 second)	7.5	Therapeutic effect in definite, minimal failure
1.5	1.0	Initiation of diuresis. Decreased dyspnea	4.5	Paroxysmal ventricular tachycardia (duration, 2 hours)	6.5	Toxicity was of brief duration and unaccompanied by nausea and vomiting
1.5	1.0	Decreased dyspnea and palpitation	3.5	Nausea	8.5	
2.0	N			Nausea and vomiting	2.0	Toxicity three hours after initial dose
1.0	1.0			Nausea	2.0	Patient digitalized two days after initial digitalization
1.5	1.0	Marked diuresis. Decreased dyspnea	2.5	Anorexia and nausea	4.5	
2.0	1.0	Diuresis. Decreased dyspnea	4.0	Anorexia and nausea	5.0	
2.0	1.0	Diuresis. Decreased dyspnea	3.0	Anorexia and nausea	6.0	
2.0	1.0	Diuresis	?	Nausea and vomiting	8.0	Therapeutic effect overshadowed by toxicity
2.0	1.0	Marked slowing of VR. Diuresis	3.0	Nausea	4.0	
2.0	1.0	Slowing of VR. Diuresis. Decreased dyspnea	4.0	Nausea	12.0	
2.0	1.0	Diuresis	6.0	Nausea and vomiting	6.0	Therapeutic effect overshadowed by toxicity
2.0	1.0			Nausea	3.0	Therapeutic effect overshadowed by toxicity

TABLE

PA-TIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS
			ETIOLOGIC	ANATOMIC	PHYSIO-LOGIC†		
14	60	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR with VPC's	+	121
15	82	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR with VPC's	N	122
16	37	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	NSR	N	154
17	66	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	Auricular flutter	++	113
18	68	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+++	149+
19	52	M	Hypertension	Enlarged heart	AF	++	204
20	64	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	Auricular flutter	N	106
21	60	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	144
22	40	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	++	197
23	64	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	N	158
24	57	M	Arteriosclerosis. Syphilis	Enlarged heart. Dilated aorta. Aortic insufficiency	NSR	+	140
25	67	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial infarct	NSR	+	115

I—CONT'D

DOSE OF DIGOXIN IN MG.		THERAPEUTIC EFFECT	THERAPEUTIC DOSE IN MG.	TOXIC EFFECT	TOXIC DOSE IN MG	REMARKS
INITIAL DOSE	DOSE EVERY SIX HOURS					
2.0	1.0	Diuresis	4.0	Anorexia and nausea	4.0	
2.0	1.0			Anorexia and nausea	4.0	
2.0	1.0			Anorexia, nausea, vomiting. Prolonged P-R interval (0.23 second)	8.0	
2.0	1.0	Change of auricular flutter to auricular fibrillation with control of VR. Diuresis	5.0	Nausea and vomiting	11.00	
2.0	1.0	Slowing of VR. Diuresis	2.0	Nausea	3.0	Condition too poor to be weighed previous to digitalization
2.0	1.0	Slowing of VR. Diuresis	5.0	Nausea and vomiting	11.0	
2.0	1.0	None		Nausea and vomiting	8.0	Increase in degree of A-V block, with no change in rhythm. Later received quinidine, with change to NSR
1.5	0.75	None		Nausea and vomiting	3.75	
1.5	0.75	Slowing of VR. Diuresis	4.5	Nausea and vomiting. Marked slowing of VR (52 per minute)	6.0	Slow VR persisted for 8 days after discontinuance of digoxin. Redigitalization with digitalis (whole leaf) produced similar therapeutic and toxic effects with 15 and 21 cat units, respectively
1.5	0.75			Nausea	12.00	
1.5	0.75	Diuresis	3.0	Nausea. Paroxysmal AF	5.25	
1.5	0.75	Diuresis	3.75	Nausea and vomiting	5.25	

TABLE

PA- TIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CON- GESTIVE HEART FAIL- URE*	WEIGHT IN POUNDS
			ETIOLOGIC	ANATOMIC	PHYSIO- LOGIC†		
26	52	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	++	154
27	64	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial in- farct	NSR Left BBB	N	147
28	31	F	Hypertension	Enlarged heart	NSR	++	262
						++	265
29	77	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+	118
30	60	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	Auricular flutter. Left BBB	+	139
31	57	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	133
32	53	F	Hypertension	Enlarged heart	Auricular flutter	++	185
33	66	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	++	99

I—CONT'D

DOSE OF DIGOXIN IN MG.		THERAPEUTIC EFFECT	THERAPEUTIC DOSE IN MG.	TOXIC EFFECT	TOXIC DOSE IN MG.	REMARKS
INITIAL DOSE	DOSE EVERY SIX HOURS					
1.5	0.75	Diuresis	3.0	Anorexia	3.75	
1.5	0.75			A-V nodal rhythm	6.0	
1.5	0.75	None		Nausea and vomiting	3.0	Patient redigitalized with digoxin five days later
1.5	0.75	Diuresis	3.0	Nausea and vomiting	4.5	
0.75	0.75	Slowing of VR	2.25	Nausea	3.75	Digitalized with digoxin intravenously four weeks previously (see Patient 9, Table IV)
2.0	1.0	Change in rhythm to auricular fibrillation	13.00	Marked slowing of VR	21.0	Digoxin was continued to a total dose of 42.75 mg. (171 cat units) without further evidence of toxicity
2.0	1.0	Disappearance of Cheyne-Stokes respiration and nocturnal dyspnea	6.0	Nausea and vomiting. A-V nodal rhythm and VPC's	8.0	
2.0	1.0	Change in rhythm to NSR	5.0	Nausea, vomiting and anorexia	9.0	
2.0	1.0	Slowing of VR. Diuresis	3.0	Nausea and vomiting	5.0	
Average†			3.75		6.0	

TABLE
 SLOW DIGITALIZATION WITH SINGLE DAILY

PA- TIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CON- GESTIVE HEART FAIL- URE*	WEIGHT IN POUNDS	DAILY DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSI- OLOGIC†			
1	45	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial in- farct	NSR	N	100	1.25
2	62	M	Arteriosclerosis. Hypertension and unknown	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Aortic insufficiency	NSR	N	139	1.50
3	67	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	N	260	1.50
4	66	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+	184	1.50
5	65	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	155	1.50
6	54	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR Right BBB	N	135	1.50
7	65	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	126	1.25
8	54	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+	108	1.00
9	59	F	Arteriosclerosis. Hypertension	Coronary sclerosis. Myocardial fibrosis. Old myocardial in- farct	NSR	+	139	1.25

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

†NSR, Normal sinus rhythm; AF, auricular fibrillation; BBB, bundle branch block; VPC, ventricular premature contraction; VR, ventricular rate.

II

DOSES OF DIGOXIN IN HOSPITALIZED PATIENTS

THER- APEUTIC EFFECT	DAYS RE- QUIRED	THER- APEUTIC DOSE IN MG.	TOXIC EFFECTS	DAYS RE- QUIRED	TOXIC DOSE IN MG.	REMARKS
			Anorexia and nausea	3	3.75	
			Anorexia and nausea	6	9.0	
			Anorexia for evening meal	3	4.5	Same dose continued for total of 7 days without further toxicity
Slowing of VR	1	1.50	Anorexia and nausea, VPC's with coupling	5	7.5	
Diuresis	3	4.5	Anorexia for evening meal, Prolonged P-R interval (0.23 second)	5	7.5	
						Patient received 1.5 mg. for 18 days without clinical evidence of toxicity at time of discharge
			Anorexia and nausea, VPC's, Prolonged P-R interval, Runs of idioventricular rhythm	4	5.0	
Slowing of VR, Diuresis	3	3.0	Anorexia for evening meal	4	4.0	
Diuresis, Slowing of VR	4	3.75	Nausea and vomiting	3	3.75	

TABLE
SLOW DIGITALIZATION WITH SINGLE DAILY

PA- TIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CON- GESTIVE HEART FAILURE*	WEIGHT IN POUNDS	DAILY DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSI- OLOGIC			
1	38	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+++	170	1.25
						+++	171	1.00
						+++	163	0.75
2	65	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Dilated aorta	AF	+++	157	1.50
						++	150	1.00
3	50	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	++	147	0.75
4	36	M	Rheumatic fever (inactive)	Enlarged heart. Mitral insufficiency. Aortic insufficiency	NSR	+	176	1.00
5	53	M	Unknown	Enlarged heart.	AF	+	167	1.50
6	25	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency. Aortic insufficiency	AF	+	150	1.00
7	61	M	Hypertension. Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial in- farct. Dilated aorta	NSR	+	144	0.75
8	75	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+	143	0.25
						+	145	0.50
9	50	M	Hypertension	Enlarged heart	NSR	+	193	1.00

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

III

DOSES OF DIGOXIN IN AMBULATORY PATIENTS

THERAPEUTIC EFFECT	WEEKS RE- QUIRED	TOXIC EFFECTS	WEEKS RE- QUIRED	REMARKS
Slowing of VR. Complete alleviation of failure. Diuresis	2			Patient discontinued medication after two weeks. Returned to clinic with heart failure six weeks later
Slowing of VR. Complete alleviation of failure. Diuresis	3			Patient continued this dose for total of 9 weeks without evidence of toxicity. Returned to clinic with heart failure 4 weeks later
None				Patient hospitalized after 1 week with persisting marked failure when he was redigitalized (see Table IV, Patient 1)
Slowing of VR. Diuresis. Complete alleviation of failure	1	VPC's with coupling	5	Medication was discontinued. Patient had moderate failure when he returned to clinic 7 weeks later
Exactly as above	1			Patient has continued this dose for over 7 weeks with no toxicity
Slowing of VR. Complete alleviation of failure	2			Patient has continued this dose for over 12 weeks without toxicity
Slow decrease in failure	6			Drug continued for 9 weeks without toxicity
Slowing of VR. Diuresis	3			Drug continued for 12 weeks without toxicity. (Patient had previously required large doses of digitalis preparations for maintenance)
Slowing of VR. Complete alleviation of failure	1	Nausea	7	
Diuresis	1	Nausea	3	
None				This dose continued for 12 weeks, then increased
Slowing of VR	3			Patient continued this dose for 9 weeks without toxicity
		Anorexia. Nausea. Vomiting		Unable to evaluate therapeutic response

TABLE
RESULTS OF DIGITALIZATION WITH

PA- TIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CON- GESTIVE HEART FAILURE*	WEIGHT IN POUNDS	DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSI- OLOGIC			
1	39	M	Rheumatic fever (inactive)	Enlarged heart. Mitral insufficiency. Mitral stenosis	AF	+++	175	1.5
2	64	M	Arteriosclerosis. Hypertension	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+++	269	1.75
3	56	M	Arteriosclerosis. Hypertension. Pulmonary fibro- sis and emphy- sema	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	NSR	+++	168	2.5
4	50	F	Hypertension	Enlarged heart	NSR	++++	150	1.5
5	58	M	Arteriosclerosis. Hypertension	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+++	188	2.5
6	71	F	Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+++	129+	1.5
7	54	M	Hypertension. Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	NSR VPC's	+++	156½	2.0

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

IV

SINGLE INTRAVENOUS DOSES OF DIGOXIN

INITIAL THERAPEUTIC EFFECT	TIME OF ON-SET	FULL THERAPEUTIC EFFECT	TIME OF ON-SET	TOXIC EFFECT	TIME OF ON-SET	REMARKS
Slowing of VR (126-96)	15 min.	Diuresis. Fall in venous pressure	24 hr.	None		
Slowing of VR (128-96)	13 min.			None		Ventricular rate remained slowed, and lowered venous pressure persisted, although no other therapeutic effect was noted for eight days. Thereafter patient improved progressively, with complete alleviation of failure on bed rest without further cardiac medication
None		None		None		Patient showed no objective or subjective improvement after administration of the drug, possibly because of pulmonary disease
Fall in venous pressure (185-142 mm. H ₂ O). Slight subjective improvement. Diuresis	14 min.	Fall in venous pressure to 118 mm. H ₂ O. Continued subjective improvement	2½ hr.	None		
Fall in VR (95-74). Fall in venous pressure (205-177 mm. H ₂ O)	10 min.	Fall in venous pressure to 38 mm. H ₂ O. Marked clinical improvement. Diuresis	21 hr.	None		
None		None		VPC's with coupling. Runs of ventricular tachycardia	17 min. 65 min.	Patient showed no improvement. Continued to have auricular fibrillation with runs of ventricular tachycardia. Became rapidly and progressively worse and died on third day after digitalization
Fall in venous pressure (118-88 mm. H ₂ O)	8 min.	Clinical improvement. Diuresis. Fall in venous pressure to 47 mm. H ₂ O. Weight loss of 7 pounds	24 hr.	None		

TABLE

PA-TIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS	DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC			
8	48	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+	142	1.5
9	77	F	Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+	118½	1.5
10	39	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency. Dilated aorta	AF	+++	145	2.0
11	51	F	Arteriosclerosis	Enlarged heart. Mitral insufficiency. Coronary sclerosis. Myocardial fibrosis	AF	++	177	2.0
12	22	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+	102	2.0
13	65	M	Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	Auricular flutter	+++	222	2.0

seven cases the therapeutic effect was indefinite, either because of the minimal degree of congestive heart failure or because it was overshadowed by toxic manifestations. In two cases the therapeutic and toxic doses were apparently identical, perhaps because digitalization took place rapidly. Three patients were not benefited from initial digitalization. No appreciable effect was noted on the auricular flutter of Patient 20, who subsequently regained normal rhythm with the help of quinidine. Patient 28 did not respond to the first course of digoxin, but five days later redigitalization with digoxin resulted in a satisfactory response. The toxic dose, with the exception of Patient 30, ranged between 2.0 and 12.0 mg. (average, 6.0 mg.). Patient 30, who had auricular flutter, required 13 mg. before a therapeutic effect could be observed, and 21 mg. over a period of five days before toxic manifestations occurred.

IV—CONT'D

INITIAL THERAPEUTIC EFFECT	TIME OF ON- SET	FULL THERAPEUTIC EFFECT	TIME OF ON- SET	TOXIC EFFECT	TIME OF ON- SET	REMARKS
Fall in VR (160-120)	15 min.	Fall in VR to 97	1 hr.	None		
	15 min.	Fall in venous pressure from 182-75 mm. H ₂ O	4 hr.			
Fall in VR (101-88)	15 min.	Fall in VR to 79. Abolition of pulse deficit. Complete symp- tomatic relief	$\frac{1}{2}$ hr.	None		
Fall in VR (119-105)	15 min.	Fall in VR to 82. Marked relief of all subjective signs.	2 $\frac{1}{2}$ hr.	None		
Fall in venous pressure (330-246 mm. H ₂ O)	60 min.	Abolition of dysp- nea and orthopnea				
Fall in VR (144-109)	15 min.	Fall in VR to 79. Marked subjective improvement	2 hr.	Nausea. Vomiting	2 $\frac{1}{2}$ hr.	
Fall in VR (120-98)	27 min.	Fall in VR to 70. Marked subjective improvement. Spontaneous sleep	1 $\frac{1}{4}$ hr.	None		
Venous pres- sure fall (128-95 mm. H ₂ O)	11 min.					Patient improved clinical- ly, with increase in de- gree of A-V block for 2 hours and 20 minutes, at which time he abruptly lost consciousness, res- piration failed, cyanosis appeared, and death en- sued within a few min- utes

The type of toxicity was in no way different from that usually observed with the whole leaf of *digitalis purpurea*. Anorexia, nausea, and vomiting were commonly the earliest manifestations. In one instance (Patient 3), a run of paroxysmal ventricular tachycardia was the only sign of toxicity. This, however, subsided rapidly when digoxin was discontinued, and did not affect the ultimate course of the patient. A change in rhythm occurred also in Patients 24 and 31, who developed auricular fibrillation and A-V nodal rhythm, respectively. These also were of short duration and disappeared spontaneously when the medication was stopped. Prolongation of the P-R interval was observed in three instances.

In the group of nine hospitalized patients (Table II) who received single daily doses of digoxin, ranging between 1.0 and 1.5 mg., it was possible to ascertain the therapeutic dose in only four cases. The others

did not have congestive heart failure at the time of digitalization. In these four cases the therapeutic dose was within the range noted for the rapid method of digitalization, but occurred, as was to be expected, a few days later. The toxic dose ranged from 3.75 to 9.0 mg. (average, 5.9 mg.). Although the same type of toxicity occurred, it was of short duration, and not as severe as that which was observed in the rapidly digitalized patients.

PATIENT 1 AGE 45 (SEE TABLE III)
 CARDIAC DIAGNOSIS
 A. HYPERTENSION
 B. ENLARGED HEART
 C. AURICULAR FIBRILLATION

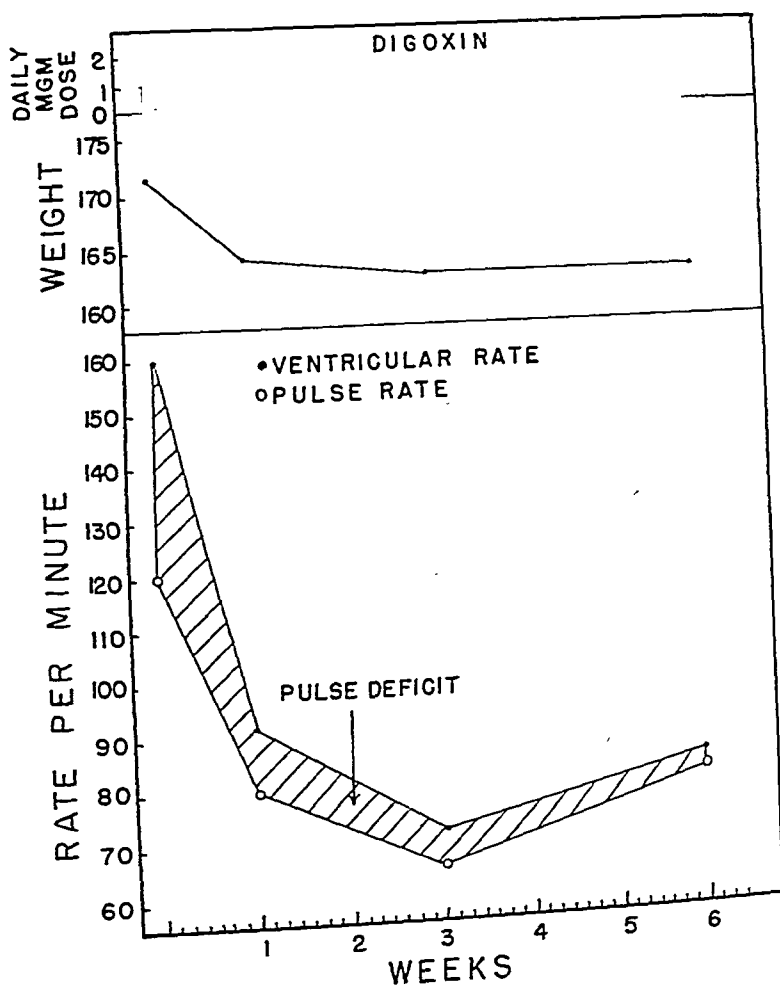


Fig. 2.—Slow digitalization achieved in an ambulatory patient with daily administration of 1.0 mg. of digoxin.

In eight of the nine ambulatory patients (Table III), slow digitalization was satisfactorily accomplished with a single daily dose of 0.50 and 1.5 mg. (Fig. 2). With the exception of Patient 4 of this group, improvement was noted within one to three weeks after the onset of therapy. It was possible to study digitalization by this method with two

trials in two cases and in three trials in another. Four patients developed toxicity. This occurred several weeks after initiating therapy, which was in contrast to the hospital group who received the same daily doses.

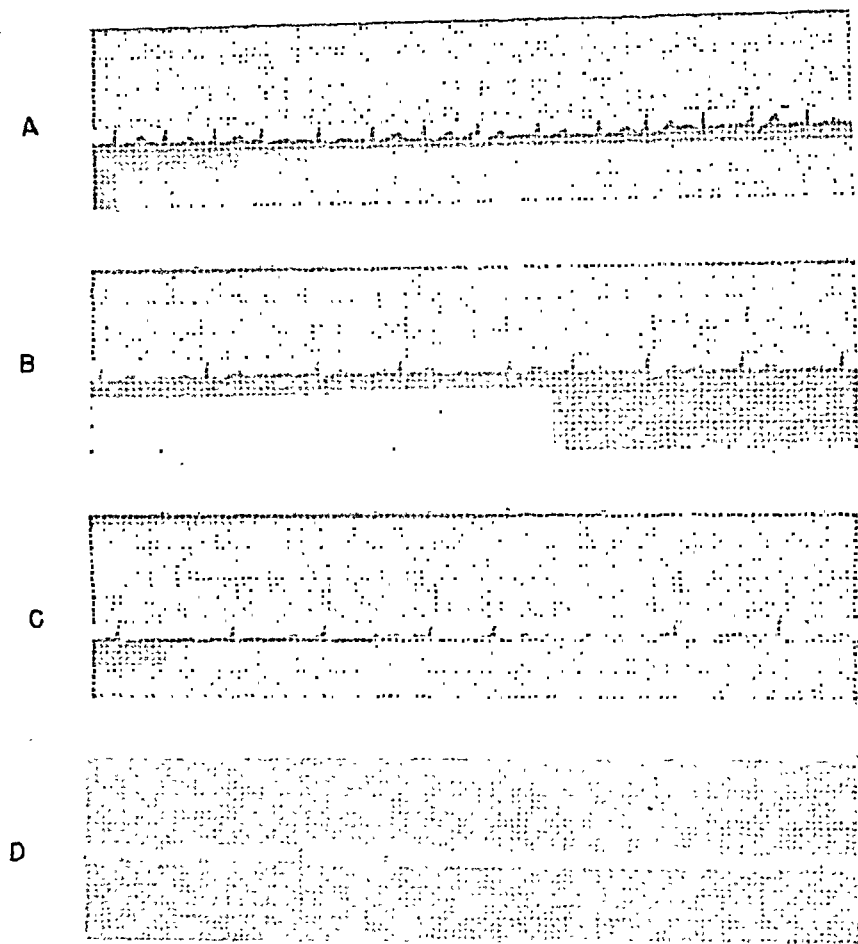


Fig. 3.—Electrocardiograms (Lead 2) of Patient 8, Table IV, with auricular fibrillation, after digitalization by means of a single intravenous dose of 1.5 mg. of digoxin. A, Control: ventricular rate, 170 per minute. B, Twenty minutes after digoxin: ventricular rate, 108 per minute. C, Forty-five minutes later: ventricular rate, 84 per minute. D, Four hours and forty-five minutes later: ventricular rate, 72 per minute.

Ten of the 13 patients who were digitalized with a single intravenous injection of digoxin (Table IV) showed objective evidence of improvement. In the group of patients with auricular fibrillation this was usually dramatic, with slowing of the ventricular rate within fifteen minutes after the drug's administration (Fig. 3). A concomitant fall in venous pressure and diuresis were also initiated, and were the best indices of effectiveness in patients with normal sinus rhythm. Patient 6, a 71-year-old woman with arteriosclerotic heart disease, developed ventricular premature systoles, with coupling, seventeen minutes after 1.5 mg. of digoxin, and subsequently developed ventricular tachycardia,

which persisted until death occurred forty-eight hours later. A second patient (Number 13), with auricular flutter, died suddenly two and one-half hours after digitalization with 2.0 mg. of digoxin intravenously. Ten of the 13 patients showed no evidence of toxicity.

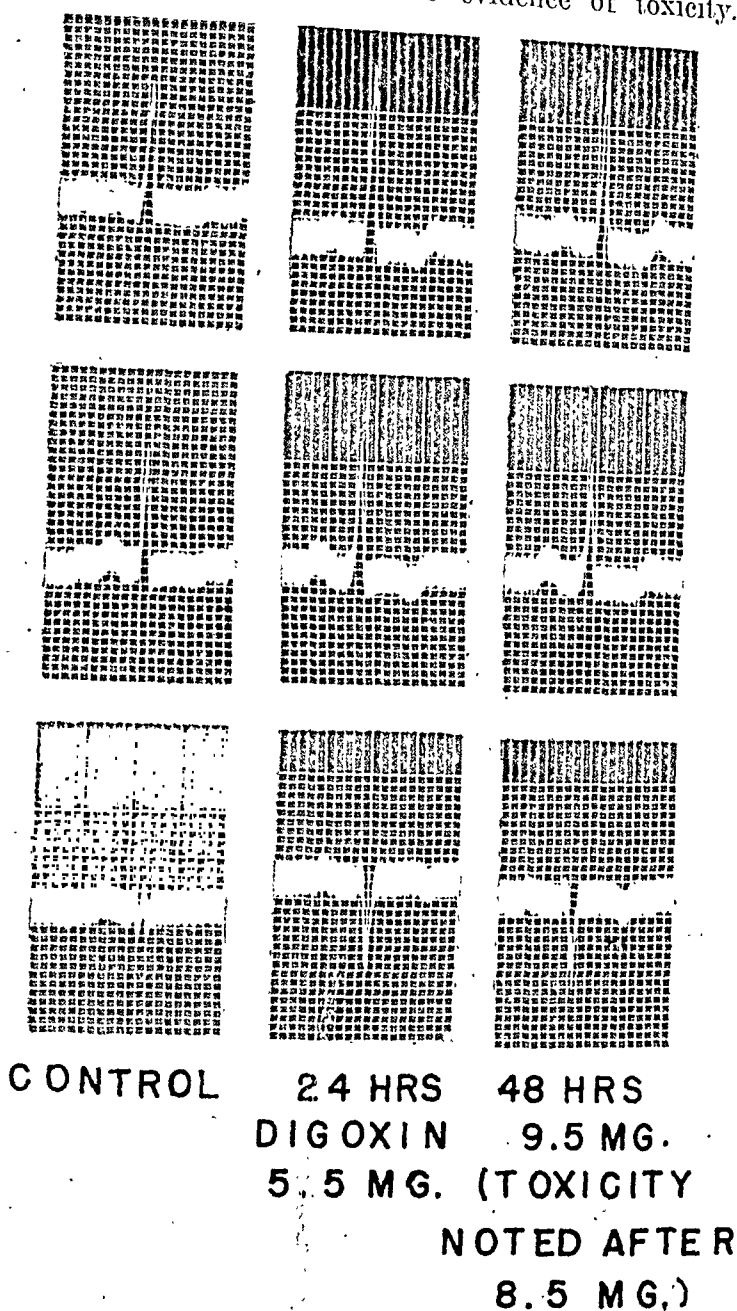


Fig. 4.—Alterations in electrocardiographic complexes produced by digitalization with digoxin orally.

Maintenance with digoxin in single daily doses was achieved in the majority of patients without difficulty. The dose varied between 0.25 and 1.5 mg.; 20 of the patients required 0.5 to 1.0 mg. In terms of cat unit potency, the patients required approximately twice as much digoxin as of digitalis leaf.

Electrocardiographic changes were noted in practically all cases, regardless of the method of digitalization. These consisted of the typical T and S-T segment depressions (Fig. 4). It was our impression that these changes were not usually as striking as those which are produced by digitalis leaf.

DISCUSSION

Digoxin was found to fulfill all of the requirements^{4b} which are demanded of a satisfactory digitalis preparation when it is given orally. The ventricular rate in patients with auricular fibrillation was controlled, and diuresis occurred in the majority of the rapidly digitalized patients within twenty-four hours. In order to compare the potency of powdered digitalis leaf with that of digoxin, it is necessary to translate the milligram dosage values of digoxin into cat units. Since 0.192 mg. of digoxin are equivalent to one cat unit, the clinical potency is the same as that of digitalis leaf. The average therapeutic and toxic doses, as ascertained by rapid digitalization, were 19.5 cat units (3.75 mg.) and 31 cat units (6.0 mg.), respectively. The ratio of toxic to therapeutic doses was also found to be similar to that of digitalis leaf. In the hospital group who were digitalized by giving large single daily doses, the toxic dose was found to be almost identical to that which was observed when the Eggleston method was used. The toxic dose was larger in the ambulatory group, who were digitalized similarly. This may have been due to the fact that observations in the ambulatory group were necessarily less frequent than in the hospital group. However, because these two groups were not large, adequate conclusions cannot be drawn.

In the ambulatory group a considerably larger dose was required for maintenance than would have been expected from the observations in the group who were rapidly digitalized by the Eggleston method; this was probably because of the rapid elimination of digoxin, which has been noticed by previous investigators.^{1a, c, 8} Schwab^{1c} stated that, because of rapid elimination, the establishment of a maintenance dosage of digoxin would be difficult. Herrmann⁸ and Schwab both estimated that the amount required for maintenance was approximately one-third of the quantity necessary to produce full digitalization. These conclusions were not supported by our study. We had no difficulty in establishing a maintenance dosage, and this was usually found to be considerably less than one-third of that estimated for full digitalization. Twelve patients of the group of 24 required 0.5 mg. or less, and only three required more than 1.0 mg. for adequate maintenance.

In the course of our study, however, we did note other indications of rapid "dissipation" of digoxin. In the rapidly digitalized group toxicity was usually of brief duration; it commonly disappeared within a few hours after discontinuance of the drug. In several patients the toxicity which was produced by initial digitalization with digoxin subsided within twenty-four to forty-eight hours, even though an adequate

daily maintenance dose of digitalis leaf was immediately given at the onset of toxicity. (This was first noted when a maintenance dose was inadvertently started on a patient who had become toxic.) The same phenomenon was observed by Fahr and LaDue⁹ with lanatoside C. In a number of patients who were digitalized with single daily doses, administered at noon, anorexia and nausea appeared only for several hours at night. These patients were able to continue taking the same daily dose for several additional days without further development of toxicity. Studies on the dissipation of digoxin are still in progress.

Digoxin was remarkably and rapidly effective when given parenterally. The therapeutic effect was evident within fifteen minutes in those patients who responded. It must be emphasized, however, that the same dangers which are inherent in the parenteral use of all digitalis preparations are present. It is never possible to predict accurately the proper individual therapeutic dose, and, therefore, when large doses are used, the possibility of causing severe toxicity and even death must be remembered. Two deaths in our series followed the administration of digoxin intravenously. One was a patient with auricular flutter whose death may well have been caused by embolism. The second was an elderly woman who had severe failure, and, therefore, rapid digitalization was thought advisable. Despite lack of clinical or electrocardiographic evidence, there is a very good possibility that her death may have been caused by concomitant myocardial infarction. Permission for autopsy was not obtained in either of these cases.

Our study indicates that the following are the proper doses of digoxin. For rapid digitalization with the oral preparation, an initial dose of 1.5 mg. should be given, followed by doses of 0.75 mg. at six-hour intervals until the desired therapeutic effect has been achieved. At this time a daily maintenance dose of 0.50 or 0.75 mg. can be given. This dose may be increased or decreased by 0.25 mg., according to the requirement of the individual patient. For digitalization with single daily doses we suggest giving 1.0 to 1.5 mg. Because our studies on the use of digoxin parenterally were done with the primary purpose of evaluating the time of onset of therapeutic response, and because we are still studying the effect of the administration of smaller amounts, we are not prepared at this time to recommend doses with this method of administration.

SUMMARY

1. The effects of digoxin, a purified crystalline glycoside which is obtained from *digitalis lanata*, were studied on 55 hospitalized and 33 ambulatory patients.
2. The average therapeutic and toxic doses with rapid administration orally were 3.75 and 6.0 mg., respectively.
3. The requirement for maintenance with digoxin was approximately twice that of *digitalis leaf*.

4. Evidences in favor of rapid dissipation of digoxin are discussed.
5. Digoxin by the parenteral route produces an effective response, usually within fifteen minutes. The inherent dangers of parenteral digitalization are considered.
6. Digoxin satisfies the established criteria for a reliable, potent digitalis preparation.

The authors acknowledge the assistance of Dr. Ludwig W. Eichna, of the Department of Medicine, New York University College of Medicine, and of several members of the resident staff of Lenox Hill Hospital, in obtaining data after the parenteral administration of digoxin.

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PERSISTENCE OF EFFECT AFTER DIGITALIZATION BY COMBINED USE OF DIGITALIS AND OUABAIN

ROBERT C. BATTERMAN, M.D., AND WILLIAM W. ENGSTROM, M.D.,
NEW YORK, N. Y.

IN A previous communication¹ the combined use of ouabain and digitalis was shown to be a satisfactory method of producing digitalization. At that time it was thought that the slowing of the ventricular rate of patients with chronic auricular fibrillation brought about by giving the two drugs together would persist longer than when ouabain was given intravenously by the method of Wyckoff and Goldring,² but for a shorter time than when digitalis leaf was administered orally by the Eggleston³ method. Since data in support of this assumption were not presented, it is the purpose of this study to compare the relative rates of dissipation of the effects of ouabain and digitalis leaf when administered alone and in combination. The relative efficacy of the three methods of digitalization will not be considered.

Since digitalis glycosides exhibit numerous and interrelated effects upon the cardiovascular system, it is possible that not all these effects persist for the same length of time in the same or different persons. The study was therefore limited to the main effects of digitalis on patients with congestive heart failure and chronic auricular fibrillation, i.e., slowing of the ventricular rate and improvement in myocardial efficiency, as manifested by relief from symptoms and signs of congestive heart failure.

SELECTION OF PATIENTS

The clinical data on the patients whom we studied are outlined in Table I. All had chronic auricular fibrillation, and, when not under the influence of digitalis, had subjective and objective evidence of congestive heart failure, and tachycardia with a ventricular rate of more than 100 per minute. These patients varied in the degree of their failure when under the influence of the drug. Some were asymptomatic with maintenance doses of digitalis. Others had moderate to severe congestive heart failure, and required diuretics, in addition to digitalis, for symptomatic relief. However, it was possible, even in such cases, to estimate the cardiac reserve, so that there was no difficulty in observing an increase in degree of failure when digitalis action had ceased. Nine of the twelve patients had inactive rheumatic heart disease and three had combined arteriosclerotic and hypertensive heart disease. Patients with myocardial infarction were excluded. All were in a chronic disease hospital where it was possible to observe them for a sufficient length of time before beginning the study, and where hospitalization could be continued long enough to complete the observations. Finally, all patients were cooperative and lent themselves well to the study.

From the Department of Therapeutics and the Department of Medicine, New York University College of Medicine, and the Third (New York University) Medical Division, Welfare Hospital for Chronic Diseases, New York City.

Received for publication Feb. 27, 1942.

TABLE I
CLINICAL DATA ON THE PATIENTS STUDIED

PATIENT	AGE	SEX	CARDIAC DIAGNOSIS		MAINTENANCE DOSE OF DIGITALIS (IN GRAMS)	SEVERITY OF HEART FAILURE*
			ETIOLOGIC	ANATOMIC		
1	39	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.1-0.2	Moderate—mild†
2	32	M	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.2-0.3	Severe
3	67	M	Arteriosclerosis Hypertension	Enlarged heart Coronary sclerosis Myocardial fibrosis	0.1	Mild
4	23	M	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency Aortic insufficiency	0.1-0.2	Moderate
5	29	M	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.1	Mild
6	39	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency Aortic insufficiency	0.2	Severe
7	36	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.2	Severe
8	54	F	Rheumatic fever Hypertension	Enlarged heart Mitral stenosis	0.1-0.2	Severe
9	57	F	Arteriosclerosis Hypertension	Enlarged heart Coronary sclerosis Myocardial fibrosis	0.1	Mild
10	38	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency Aortic insufficiency	0.1	Moderate
11	80	F	Arteriosclerosis Hypertension	Enlarged heart Coronary sclerosis Myocardial fibrosis	0.05-0.1	Mild
12	15	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.1-0.2	Moderate

*The estimation of the degree of the congestive heart failure was based upon the severity of the symptoms and signs of failure which the patient presented when not under the influence of digitalis, and upon the degree to which these symptoms were relieved by digitalization or maintenance doses of digitalis.

†In this patient the symptoms were of moderate failure early in the study; later her symptoms became definitely milder.

METHOD

During a preliminary control period which ranged from one to several months, the effectiveness of a maintenance dose of digitalis leaf was observed in order to estimate the cardiac reserve, i.e., the degree of compensation which could be obtained with the drug, in conjunction with rest in bed and limitation of fluid intake. Digitalis was then discontinued, and the patients were observed daily for signs and symptoms of development of, or an increase of, congestive heart failure and tachycardia. When this state occurred and persisted in bed, the patients were

rapidly and fully digitalized by one of three methods. The procedure was then repeated, but digitalization was performed each time by a different method. However, regardless of the method used, no more digitalis or ouabain was given until all the effects of the previous digitalization had disappeared. In this way nine of the twelve patients were digitalized more than once by each method. Twenty-one digitalizations were done with ouabain alone, twenty with the combined drugs, and sixteen with digitalis leaf alone.

The method of Wyckoff and Goldring² was used for digitalization with ouabain alone. An initial dose of 0.5 mg. (5 cat units) of ouabain* was given intravenously, followed by successive doses of 0.1 mg. every half-hour or every hour until toxic signs appeared or the ventricular rate fell below 70 per minute. The combined use of ouabain and digitalis, as previously reported,¹ consisted of administering 0.5 mg. of ouabain intravenously simultaneously with 0.4 to 0.8 grams (4 to 8 cat units) of digitalis leaf* orally. The third method was that recommended by Eggleston,³ and consisted of giving, initially, one-half of the total estimated dose, and the remainder in divided doses every six hours. Since we had had previous experience with the ouabain and digitalis leaf preparations which were used, it was relatively easy to ascertain the amount of each drug each patient would require to obtain the full effect. Since, cat unit for cat unit, ouabain is twice as potent in man as digitalis leaf, the appropriate dose of either preparation was known after the first digitalization with either drug alone.

Before each digitalization an effort was made to allow the original degree of congestive heart failure and tachycardia to return. Also, we attempted to maintain a constant level of digitalization by administering the drugs in doses sufficient to produce, for each comparison, a similar degree of toxicity. In this manner any question of insufficient or inconsistent dosage was obviated as far as possible.

All of the patients were given the same general diet, and the salt and fluid intake was kept as constant as possible. The majority of the patients were kept continually in bed; several were semiambulatory when they did not have failure. However, in each case, a constant degree of activity was maintained. Each patient was examined daily for evidences of congestive heart failure, and carefully questioned as to subjective symptoms, such as dyspnea, orthopnea, palpitation, and pain in the liver area. The ventricular and radial pulse rates, counted for one minute, were recorded daily, or more frequently when indicated. The patients were weighed daily, and blood pressures were recorded at frequent intervals. Electrocardiograms were taken several times during the control period, twenty-four hours after each digitalization, and every third or fourth day thereafter.

During the course of the study, it soon became apparent that factors other than the digitalis preparation or method of digitalization influenced the persistence of the digitalis effect in a given case. For example, any alteration in the degree of the congestive heart failure, produced either by mercurial diuretics or by mechanical means, such as paracentesis, would greatly influence the ventricular rate. For this reason, while we were comparing the effects of the three methods, those factors which might alter the cardiovascular status of the patient were avoided or excluded from the study. However, in two instances (patients 1 and 8) such a change in status occurred, but because the change was between the series of comparisons and did not occur while comparing the methods with one another, the results are included.

*Ampules of ouabain, in a concentration of 2.5 cat units per cubic centimeter, and tablets of digitalis (whole leaf), of multiple cat unit strength, were supplied by Carroll Dunham Smith Pharmacal Company, Orange, New Jersey. The potency of these preparations was confirmed in our laboratory by the Hatcher and Brody method of assay.

RESULTS

The details of the individual digitalizations are summarized in Table II. The results are considered in three categories, namely, the time, in days, required for the reappearance of congestive heart failure, the development of tachycardia (ventricular rate 100 or over), and a precipitous rise of the ventricular rate to a level usually associated with uncontrolled auricular fibrillation. On the average, these reappeared earliest after digitalization with ouabain alone, next with combined ouabain and digitalis, and last with digitalis alone. The means and their standard errors for each method of digitalization are presented in Table III.

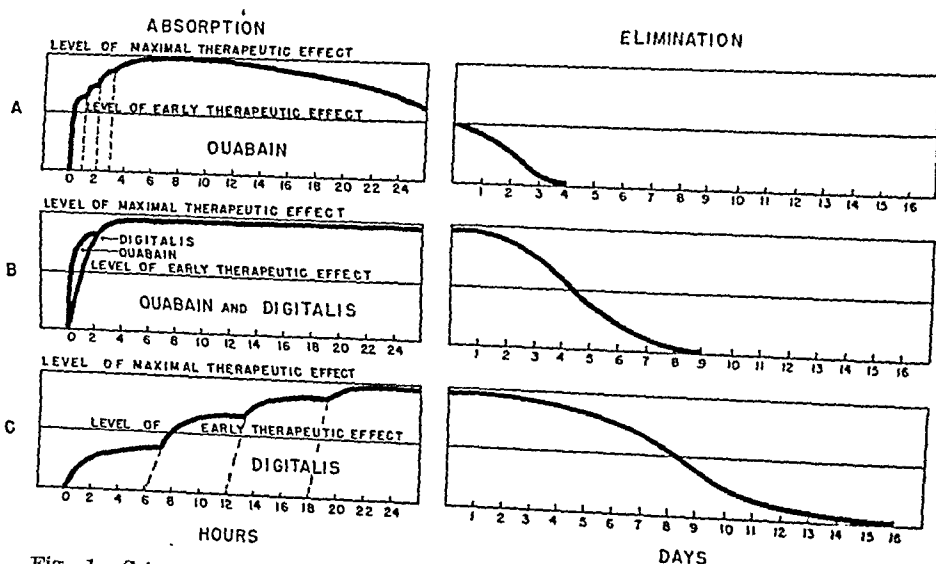


Fig. 1.—Schematic representation of absorption and elimination: A, of ouabain given intravenously by the method of Wyckoff and Goldring; B, digitalis and ouabain in combination by the method of Batterman, Rose, and DeGraff; and C, digitalis leaf given orally by the method of Eggleston. (By elimination is meant the persistence of digitalis effect upon the ventricular rate of patients with auricular fibrillation.)

Calculation of Fisher's *t*-function indicates that the differences between the three sets of means are highly significant, and cannot be ascribed to sampling errors. It should be noted that these data are based upon fifty-seven digitalizations of twelve patients. This group is too small to show that there is less variation among trials carried out upon the same patient than there is for the whole group. Other factors than the drugs used or method of digitalization may influence the persistence of the effect. For instance, it is probable that in a few instances a sudden alteration in the cardiovascular status occurred which was beyond our control. The patient's cardiac reserve, or its clinical counterpart, the degree of congestive heart failure, also constituted a source of variation.

To complete the schematic presentation of data on absorption and elimination with each method, as shown in the previous communication,¹ Fig. 1 is included.

SUMMARY OF RESULTS ON PERSISTENCE OF DIGITALIZATION WITH THE THREE METHODS DESCRIBED IN TEXT

TABLE II

PATIENT	TRIAL	METHOD OF DIGITALIZATION	DOSE IN CAT UNITS*	STATUS AT TIME OF DIGITALIZATION		EVIDENCE OF FULL DIGITALIZATION		TIME IN DAYS FOR RE-APPEARANCE OR INCREASE IN CONGESTIVE HEART FAILURE	VENTRICULAR RATE AT ONSET OF CONGESTIVE HEART FAILURE	TIME IN DAYS FOR VENTRICULAR RATE TO EXCEED 100 PER MINUTE	TIME IN DAYS FOR RE-APPEARANCE OF PRECIPITOUS RISE IN VENTRICULAR RATE	REMARKS
				WEIGHT IN POUNDS	VENTRICULAR RATE	CLINICAL	VENTRICULAR RATE					
1	1	Ouabain	6	117½	148	Nausea Vomiting	58	3	88	4	5	Two days after first signs of failure apical rate rose to 132
	2	Ouabain and digitalis	9	118½	146	Nausea Vomiting	66	4	90-94	5	5	One day after first signs of failure apical rate rose to 126
	3	Digitalis	12	118	142	Anorexia Nausea	60	6	96	7	7	
	4	Ouabain	6	108¾	132	Anorexia Nausea	67	9	106	9	10	Between the third and fourth trials patient spontaneously lost all edema with a weight loss of ten pounds
2	5	Ouabain and digitalis	9	110	138	Nausea Vomiting	66	10	106	10	13	
	6	Digitalis	12	112½	136	Anorexia Nausea	70	19	128	19	19	Failure and sudden tachycardia occurred simultaneously
	7	Ouabain and digitalis	9	111	134	Nausea	68	15	112	15	17	
	1	Ouabain	7	126½	120	Nausea Headache	70	3	110	3	4	Failure noted with apical rate of 110. Precipitous rise occurred following day
	2	Ouabain and digitalis	11	125½	128	Anorexia Nausea	70	5	120	5	5	Failure and sudden tachycardia occurred simultaneously

*In the combined method of digitalization, 0.5 mg. (equivalent to 5 cat units) of ouabain was used in every instance except in case 12, in which 0.3 mg. was administered. This patient was 15 years of age and weighed only 72 pounds.

†This patient expired suddenly seven hours after the administration of 0.7 mg. (divided doses) of ouabain intravenously. Autopsy revealed typical healed rheumatic lesions of aortic and mitral valves and an anomaly of the left coronary artery, but no immediate cause of death was found.

2	3	Digitalis	14	125	130	Nausea	75	8	112	8	11	Sudden tachycardia occurred three days after signs of failure, and rate of 100 per minute appeared
	4	Ouabain	7	124½	130	Nausea Headache Dizziness	68	14	108	4	5	Failure and sudden tachycardia appeared simultaneously
	5	Ouabain and digitalis	11	125½	135	Nausea Vomiting	68	6	142	6	6	
	1	Ouabain	7	165½	120	Nausea Anorexia	66	3	92	4	5	
3	2	Ouabain and digitalis	11	165	121	Anorexia	63	12	116	10	12	Although rate exceeded 100 on the tenth day, it fell again only to rise suddenly on the twelfth day, accompanied by failure
	3	Digitalis	14	171	122	Nausea Anorexia Extrasystoles	70	27	110	27	29	
	1	Ouabain	7	118¼	136	Anorexia Nausea	66	3	112	3	4	
4†	2	Ouabain and digitalis	11	120	140	Nausea Vomiting	66	6	108	6	11	For five days rate ranged between 106 and 120 before suddenly rising to 146
	3	Digitalis	14	120	136	Nausea Vomiting	60	14	142	9	14	Unable to detect any sign of failure while rate ranged between 104 and 114. Rise to 142 was sudden
	4	Ouabain and digitalis	11	118	146	Nausea	74	10	143	8	10	Unable to detect failure before rate rose suddenly to 143
	5	Digitalis	14	117¾	140	Nausea Anorexia	68	15	122	12	15	Unable to detect failure with rate from 96 to 112

REMARKS

PATIENT	TRIAL	METHOD OF DIGITALI- ZATION	DOSE IN CAT UNITS*	STATUS AT TIME OF DIGI- TALIZATION		EVIDENCE OF FULL DIGITALIZATION		TIME IN DAYS FOR RE- APPEAR- ANCE OR INCREASE IN CON- GESTIVE HEART FAILURE	VENTRIC- ULAR RATE AT ONSET OF CON- GESTIVE HEART FAILURE	TIME IN DAYS FOR VEN- TRICULAR RATE TO EXCEED 100 PER MINUTE	TIME IN DAYS FOR APPEAR- ANCE OF PRECIPI- TIOUS RISE IN VENTRIC- ULAR RATE	REMARKS
				WEIGHT IN POUNDS	VEN- TRICU- LAR RATE	CLINICAL	VEN- TRICU- LAR RATE					
5	1	Ouabain	7	135	118	Anorexia Nausea	69	5	108	5	8	
	2	Ouabain and digitalis	11	134½	116	Anorexia Nausea Extrasystoles	62	14	114	12	14	Rate exceeded 100 on twelfth day only to fall and rise suddenly accompanied by failure on 14th day
	3	Digitalis	14	134½	116	Nausea	70	28	98	29	29	Precipitous rise one day after failure appeared
	4	Ouabain	7	136½	126	Anorexia Nausea	60	4	108	4	7	
6	1	Ouabain	6	141¾	118	Nausea Vomiting	68	3	86	4	4	Rate suddenly rose to 118 the day after failure was de- tected
	2	Ouabain and digitalis	9	147¼	128	Nausea Vomiting	51	6	124	6	6	Rate rose suddenly overnight from 82 to 124
	3	Digitalis	12	145	132	Anorexia	62	11	112	11	11	
	4	Ouabain	6	141¾	118	Nausea Vomiting	60	4	108	4	4	Rate rose suddenly overnight from 70 to 108
	5	Ouabain and digitalis	9	145¾	124	Nausea Vomiting	62	5	132	5	5	
	6	Digitalis	12	145¾	119	Anorexia Nausea	60	11	86	12	12	Definite signs of failure noted with rate of 86
7	1	Ouabain	7	128	120	Nausea Vomiting Coupling	48	3	87	3	3	Failure noted in morning with rate of 87. In afternoon rate rose suddenly to 112
	2	Ouabain and digitalis	9	123¾	154	Nausea Anorexia	60	4	80	6	6	Patient had slight temperature elevation at this time
	3	Ouabain	7	122	144	Nausea Vomiting	48	4	90	5	5	

8	1	Ouabain	7	120 1/4	126	Nausea Vomiting Extrasystoles	75	3	96-108	3	3	Rate rose overnight from 70 to 106, with a three pound weight gain
	2	Ouabain and digitalis	11	120	134	Nausea Vomiting Extrasystoles	68	3	106	3	3	Following digitalization done after abdominal paracentesis
	3	Digitalis	14	118 1/4	122	Nausea Headache Vomiting Coupling	70	8	110	8	8	Sudden rise from 86 to 108 without previous evidence of increased failure
	4	Ouabain	7	111	126	Anorexia Nausea	66	5	108	5	5	For two days rate ranged between 100 and 106 before failure was noted
	5	Ouabain and digitalis	11	106 3/4	138	Nausea Vomiting Extrasystoles	72	9	108	7	10	Rate over 100 for three days before failure was noted
	6	Digitalis	14	111 1/4	120	Nausea Vomiting Extrasystoles	60	14	118	14	14	Rate over 100 for three days before failure was noted
9	1	Ouabain	7	156	138	Anorexia Nausea	67	7	126	4	4	Rate over 100 for three days before failure was noted
	2	Ouabain and digitalis	11	150	148	Nausea Vomiting	70	37	130	34	36	Sudden overnight rise from 94
	3	Digitalis	14	151	122	Nausea Vomiting	76	37	120	37	37	
	4	Ouabain	7	150	132	Anorexia Nausea	68	7	126	3	7	
	5	Ouabain and digitalis	11	150	132	Nausea	69	24	120	22	22	Sudden rise in rate on twenty-second day from 70 to 110 without noting failure
10	1	Ouabain	6	121 1/2	114	Anorexia Nausea	66	11	124	11	11	Sudden rise overnight, with failure
	2	Ouabain and digitalis	9	125	120	Nausea Vomiting Extrasystoles	52	12	80	12	12	Failure noted in morning with rate of 80. In afternoon rate rose suddenly to 116
	3	Digitalis	12	120	116	Nausea Anorexia	41	28	114	28	28	Sudden rise from 82 to 114 overnight

TABLE II—CONT'D

PATIENT	TRIAL	METHOD OF DIGITALIZATION	DOSE IN CAT UNITS*	STATUS AT TIME OF DIGITALIZATION		EVIDENCE OF FULL DIGITALIZATION		TIME IN DAYS FOR REAPPEARANCE OR INCREASE IN CONGESTIVE HEART FAILURE	VENTRICULAR RATE AT ONSET OF CONGESTIVE HEART FAILURE	TIME IN DAYS FOR VENTRICULAR RATE TO EXCEED 100 PER MINUTE	TIME IN DAYS FOR REAPPEARANCE OF PREVIOUS RISE IN VENTRICULAR RATE	REMARKS
				WEIGHT IN POUNDS	VENTRICULAR RATE	CLINICAL	VENTRICULAR RATE					
11	1	Ouabain	7	111½	128	Anorexia Nausea Extrasystoles	86	7	120	2	2	For five days rate above 100 but below 120 without signs of failure
	2	Ouabain and digitalis	11	111	122	Anorexia Nausea Extrasystoles	82	15	126	6	6	For nine days rate above 100 but below 126 without signs of failure
11	3	Digitalis	14	110½	132	Anorexia Nausea	66	27	122	13	9	For fourteen days rate above 100, but below 122 without signs of failure
	4	Ouabain	7	113	126	Nausea Vomiting	76	6	120	2	2	For four days rate over 100, but below 120 without signs of failure
12	1	Ouabain	5	72½	134	Nausea Vomiting	72	5	164	4	5	No failure with rate of 108. Sudden rise overnight to 164
	2	Ouabain and digitalis	7	70½	164	Nausea Vomiting	76	6	118	6	7	
	3	Digitalis	10	73	146	Nausea Vomiting	68	11	112	11	12	
	4	Ouabain	5	73½	148	Nausea Vomiting	65	4	138	4	4	On afternoon of eighth day rate suddenly rose to 144
	5	Ouabain and digitalis	7	72½	138	Nausea Vomiting	64	8	112	8	8	On afternoon of twelfth day rate suddenly rose to 138
	6	Digitalis	10	72	144	Nausea Vomiting	64	12	114	12	12	

TABLE III

ORIGINAL DEGREE OF CON- GESTIVE HEART FAILURE	MEAN TIME IN DAYS REAPPEARANCE OF HEART FAILURE			MEAN TIME IN DAYS REAPPEARANCE OF TACHYCARDIA			MEAN TIME IN DAYS FOR REAPPEARANCE OF PRECIPITOUS RISE IN VENTRICULAR RATE		
	OUABAIN	OUABAIN AND DIGITALIS	DIGITALIS	OUABAIN	OUABAIN AND DIGITALIS	DIGITALIS	OUABAIN	OUABAIN AND DIGITALIS	DIGITALIS
Mild	6	18	28	4	15	25	6	17	28
Moderate	5	8	14	5	7	13	6	9	15
Severe	4	5	10	4	5	11	4	6	11
All degrees of failure ± standard error	4.9 ± 0.5	10.5 ± 1.8	17.2 ± 2.3	4.3 ± 0.5	9.6 ± 1.6	16.1 ± 2.3	5.1 ± 0.5	10.7 ± 1.7	17.2 ± 2.3
Total number of digi- talizations by each method	21	20	16	21	20	16	21	20	16

The twelve patients are grouped with regard to degree of congestive heart failure, and the mean time is given in days for the persistence of digitalis effect by the three methods of digitalization. At the bottom of the table is given the mean time for all original degrees of failure with their standard errors and the number of digitalizations on which the results are based.

The patients with severe failure exhibited a shorter duration of digitalis action by any method of digitalization than did those with milder symptoms of diminished cardiac reserve (Table III). This is well illustrated by patients 1 and 8 (Table II), who had altered their cardiac status during the study. When patient 1 had severe failure, signs and symptoms reappeared in three, four, and six days after digitalization with each method, respectively, and nine, ten, and nineteen days, respectively, when compensation occurred spontaneously.

Whether other factors, such as age, sex, or type of heart disease, were significant in determining the persistence of the digitalis effect could not be concluded from this study.

Since an investigation of this sort affords an ideal opportunity for an analysis of the course of events from the time of full digitalization to the period of congestive heart failure, it is of interest to consider the frequency with which symptoms and signs of heart failure precede the recurrence of tachycardia and the precipitous rise in ventricular rate (Table IV). In 21 per cent of the trials, failure preceded the rapid ventricular rate, and in 50 per cent of the trials, failure appeared before the precipitous increase in rate.

TABLE IV

THE APPEARANCE OR INCREASE OF CONGESTIVE HEART FAILURE	NUMBER OF INSTANCES	PER CENT OF DIGITALIZATIONS
Before tachycardia (rate over 100) occurred	12	21
Simultaneously with tachycardia	31	55
After tachycardia occurred	14	24
Before precipitous rise in ventricular rate occurred	27	48
Simultaneously with precipitous rise	23	41
After precipitous rise occurred	6	11

The percentage of all digitalizations in which symptoms and signs of heart failure precede, occur simultaneously with, or follow, the recurrence of tachycardia and the precipitous rise in ventricular rate.

COMMENT

It should be made clear that this study was limited to patients with chronic auricular fibrillation who, when not under the influence of digitalis, showed signs and symptoms of congestive heart failure and tachycardia. Whether or not similar results would be obtained with other forms of heart disease which have different characteristics must await further investigation.

As might be expected on theoretical grounds, the duration of the effect of ouabain and digitalis in combination was intermediate between that of ouabain alone and that of digitalis alone. Thus, ouabain maintained a slow ventricular rate for a mean period of 4.3 days, ouabain and digitalis, for 9.6 days, and digitalis leaf, for 16.1 days. It should be emphasized that what is being measured in this study is not actual elimination of the drugs, but persistence of their effect.

Cognizance of this difference was stressed by Gold,⁴ and is the basis for explaining in part the variations noted in the same or different persons. It is well known that, after initial digitalization with ouabain, a patient can tolerate, within 24 hours, a subsequent dose of ouabain or digitalis leaf as if no ouabain had been given previously. This would indicate rapid elimination of the drug, and yet the initial digitalization will last, on the average, for four days. Although the elimination of digitalis leaf is much slower, as demonstrated by Pardee⁵ and Gold,⁴ it is conceivable that here also the effect will outlast the actual elimination of the drug.

Abundant evidence, both clinical and laboratory, has accumulated to attest the fundamental actions of digitalis—an increase in the force of systolic contraction⁶ and an increase of the mechanical efficiency of the heart muscle.⁷ This brings about restoration to normal function and improvement in the cardiac reserve and compensation within the limits of the severity of the heart disease. Previous studies on the persistence of this action of digitalis are lacking chiefly because undue emphasis has been placed on the ventricular rate. Considering, therefore, the reappearance of congestive heart failure, the action of ouabain will persist on the average for 4.9 days, that of ouabain and digitalis combined for 10.5 days, and that of digitalis leaf for 17.2 days.

That great variation in the persistence of the digitalis effect occurs not only in different persons but also in the same person at different times is clear from the earlier studies,^{2, 8} and also from our investigation. The patients who had the most severe heart failure, who required, in general, a larger dose of digitalis for maintenance, and who usually showed some signs of decompensation when they were fully digitalized exhibited a shorter duration of effect than did those with milder symptoms of failure and a better cardiac reserve. This is probably one of the important reasons why differences in persistence of effect are observed in different patients, even though they are digitalized to the same degree and by the same method. However, other factors certainly are present. Although the work of Boas⁹ was not directly concerned with the persistence of digitalis effects, the factor of disturbed "vagus accelerator balance," which occurs in fever and hyperthyroidism, probably is another reason for variations in duration of effect.

The relationship of the recurrence of heart failure to tachycardia is of particular interest in view of the present concept¹⁰ that the slowing of the ventricular rate is primarily due to improvement of the circulation and secondarily to depression of the conducting system. Thus, slowing of the ventricular rate has been attributed to reflex stimulation of the vagus when compensation is restored. It is to be expected, therefore, that when the process is reversed, tachycardia should occur in the effort to maintain an adequate circulation. At first glance our results might not appear to support this interpretation, for,

on the average, tachycardia and congestive heart failure seemed to recur at the same time. However, on closer analysis, when the course of events are grouped together, regardless of previous method of digitalization, in only 24 per cent of the cases did tachycardia occur before failure reappeared. In an almost identical number of instances, 21 per cent, failure preceded the tachycardia, whereas, in 55 per cent, it seemed to occur simultaneously. Furthermore, when one considers a very rapid ventricular rate usually found in uncontrolled auricular fibrillation, failure preceded this state in almost half of the instances, and in only 11 per cent of the digitalizations was this reversed. However, when each patient is considered individually, there is no adequate means of ascertaining what the optimum ventricular rate for compensation should be. The appearance of failure with a rate of less than 100 per minute might signify that this rate was a "tachycardia" for this patient, and therefore detrimental to myocardial efficiency. Nevertheless, it is our belief that the dissipation of the effects of digitalization occurs in the following order. First, there is a gradual increase in the ventricular rate as the myocardial and vagal components of the digitalis action progressively decrease. The heart then responds at a rate compatible with the demands of the underlying cardiac reserve. As the myocardial effects of digitalis diminish, or because the increased ventricular rate places an added burden upon the heart, the patient develops signs and symptoms of congestive heart failure. This initiates a reflex mechanism which causes a further rise in the ventricular rate in an effort to maintain the circulation. Such an explanation would account for the "tachycardia" which occurs in many instances before the onset of failure, whereas an "uncontrolled" rapid ventricular rate in the majority of instances occurs "simultaneously" or after the development of failure.

SUMMARY

1. Digitalization with ouabain, digitalis alone, and with the two in combination was carried out twenty-one, sixteen, and twenty times, respectively, in twelve patients with chronic auricular fibrillation.

2. The persistence of the effect upon the ventricular rate and control of the congestive heart failure were shortest after digitalization with ouabain alone, longer with ouabain and digitalis combined, and longest with digitalis alone.

3. The digitalis action was shortest by any method of digitalization in the patients who had severe congestive heart failure.

4. The relationship between the rapid ventricular rate of auricular fibrillation and congestive heart failure is discussed.

The authors wish to express their appreciation to Dr. J. Murray Steele, Director of Third Medical Division, Welfare Hospital, for his valuable suggestions and criticisms; and to Dr. Robert A. Lehman for the statistical analysis of the results.

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AN ELECTROCARDIOGRAPHIC AND CLINICAL STUDY OF LANATOSIDE C

R. M. TANDOWSKY, M.D.
LOS ANGELES, CALIF.

RECENT clinical studies¹ have demonstrated the rapidity with which lanatoside C acts in the presence of congestive heart failure. These studies, however, do not include graphic or definite substantiating physical evidence.

It was the purpose of this investigation to compare, electrocardiographically, the effect on the myocardium of lanatoside C intravenously with that of digitalis purpurea by mouth. Many are of the opinion that the action of orally administered digitalis purpurea is for the most part sufficiently rapid, as compared with that of a glucoside given intravenously. It has been shown repeatedly that intravenous therapy is desirable for patients who are suffering from gastrointestinal disturbances, or are in extremis, when the absorption of a drug such as digitalis is definitely slowed. In the latter instance the time element may be an important factor in therapy. Recent observations by Fahr and LaDue and others²⁻⁶ have demonstrated that the rapid clinical effectiveness and low toxicity of lanatoside C are due to its chemical composition. In view of these observations it was felt that electrocardiographic study of patients who were receiving this drug might offer additional confirmation of a digitalis effect.

Lanatoside C is one of the three crystalline, stable, initial glycosides of digitalis lanata. It has no counterpart in digitalis purpurea, and occurs only in the lanata plant. The exact relationship between digitalis purpurea and digitalis lanata has been elucidated by the extensive studies of Stoll.⁷ He has shown that the hitherto best known glycosides of digitalis purpurea, digitoxin and gitoxin, are products of degradation which have lost one acetyl and one glucose molecule. Digitalis glycosides consist of aglycones, chemically bound to a varying number of sugars. Smith⁸ has shown that the aglycone of lanatoside C differs from the other aglycones (genins) of digitalis purpurea and lanata. Although the aglycones possess the cardioactive properties, the sugar components appear to influence absorbability and fixation power. Therefore, it was felt that electrocardiographic observations should be made, for it is known that different preparations of digitalis vary somewhat. Rothlin,⁹ Chen and co-workers,¹⁰ and others have shown experimentally that the

From the medical wards of the Los Angeles General Hospital, College of Medical Evangelists' Division.

Lanatoside C is marketed by Sandoz Chemical Works, Inc., under the name of Cedilanid.

Received for publication Feb. 13, 1942.

pharmacologic effectiveness of these glycosides is enhanced by increasing the sugar content. Visser and Peters¹¹ measured the energy metabolism of the heart and showed that lanatoside C increases the mechanical efficiency of the failing heart more rapidly and with a greater margin of safety than other preparations.

The cat unit assay (Hatcher Brody method) was ignored in this investigation, because recent studies by Gold and his associates¹² have clearly shown that cat units are no indication of the therapeutic potency of digitalis in man. Moreover, since lanatoside C is a pure crystalline substance, biologic assay is not necessary.

LaDue^{13, 14} has shown that lanatoside C can be given in therapeutic doses to human beings over a long period of time without danger of producing morphologic changes in the myocardium. This has been confirmed experimentally by the fact that, when complete digitalizing doses were given intravenously to dogs every day for thirty days, the heart muscle was found to be histologically normal. This observation led to the bold method of administration used in this study, namely, the one-unit dosage.

MATERIAL AND METHODS OF STUDY

The criteria of a digitalis effect were the time necessary to obtain maximal depression of the RS-T segment in Lead II of the electrocardiogram, the rapidity with which the signs and symptoms of congestive failure disappeared, and the time required for the abolition of the segment changes. The standard digitalis purpurea leaf (U.S.P.) was used in one group because it is routinely used in our wards at the General Hospital.

Normal Controls.—Each of two normal, healthy adults received 1.6 mg. (S c.c.) of lanatoside C intravenously over a period of sixty seconds, and two others were given 16 grains of digitalis purpurea leaf orally on a fasting stomach in a single dose. Four-lead electrocardiograms were recorded prior to the administration, and at intervals of fifteen minutes thereafter for a period of two hours. Further tracings were taken at varying intervals for as long as seventy-two hours.

Congestive Failure.—Forty patients with congestive failure were divided into two groups, irrespective of age, etiology, or severity of the congestive failure. The patients in one group received 16 grains of digitalis purpurea orally, and those in the other group received a single dose of 1.6 mg. of lanatoside C intravenously. Electrocardiograms were recorded in a like manner, and the response was observed clinically.

Particular attention was given to the incidence of toxic effects. Because of the severity of the congestive failure in some cases it was sometimes impossible to continue this study over a prolonged period of time. In such cases, or when complications required other methods of therapy, these were instituted.

RESULTS

In the two normal controls who received lanatoside C, the maximal depression of the RS-T segment occurred in thirty minutes in one, and in twenty-five minutes in the other (Table I and Fig. 1). A digitalis effect, however, was first noted in the electrocardiogram approximately fifteen minutes after the injection of lanatoside C, as manifested by a slight depression of the RS-T segment. Throughout the entire period

TABLE I

COMPARATIVE EFFECTS OF LANATOSIDE C (1.6 MG. I.V.) AND WHOLE LEAF OF DIGITALIS PURPUREA (1.2 GM. ORALLY) ON RS-T SEGMENT AND HEART RATE

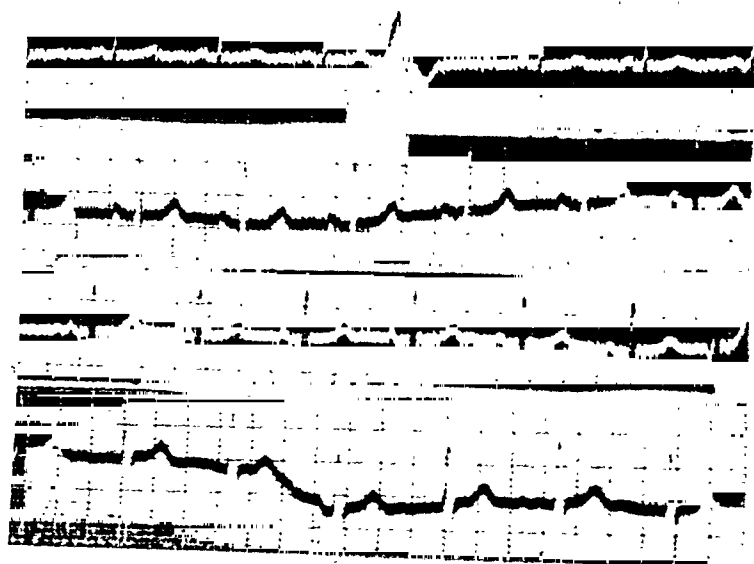
MAXIMUM RS-T SEGMENT CHANGE		MAXIMUM SLOWING EFFECT ON HEART RATE			
<i>Patients Receiving Lanatoside C</i> (1.6 mg. I.V.)		<i>Patients Receiving Lanatoside C</i> (1.6 mg. I.V.)			
<i>Control Normals</i>		<i>Control Normals</i>			
A. 30 min. } Aver. maximum RS-T		A. 20 minutes from 86 to 80 } Average			
B. 25 min. } change = 27.5 min.		B. 15 minutes from 78 to 66 } 17½ min.			
<i>Patients With Congestive Failure</i>		Maximum pulse reduction determined at one-hour intervals during 24 hours.			
NO.	HOURS	NO.	TIME	FROM	TO
1	1½	1	3 hr. 40 min.	180§R	80
2	5½	2	2 hr. 30 min.	108	62
3*	8	3	4 hr.	140	78
4	2½	4	4 hr.	156	74
5	2	5	5 hr.	100§	72
6†	3½	6	2 hr.	130§R	105
7	2	7	2 hr. 10 min.	116	140
8	3½	8	3 hr.	150§	86
9	2½	9	3 hr.	110	80
10‡	4	10	4 hr.	150§R	84
11	3	11	3 hr. 30 min.	120§	70
12	3	12	2 hr. 30 min.	114§	90
13	1½	13	3 hr. 30 min.	150	88
14	4	14	3 hr. 15 min.	86§	82
15	4	15	5 hr. 30 min.	108§	62
16	2½	16	5 hr.	120	70
17	4	17	4 hr. 10 min.	116	90
18	1½	18	— 30 min.	120	110
19	2½	19	2 hr. 30 min.	96	80
20	2	20	2 hr.	100	88
Average time for maximum RS-T change 3 hours 6½ minutes. Without Case No. 3, 2 hours 45 minutes		Average			
		123.5 80.4			
<i>Patients Receiving Digitalis Purpurea</i> (1.2 Gm. orally)		<i>Patients Receiving Digitalis Purpurea</i> (1.2 Gm.)			
<i>Control Normals</i>		<i>Effect Heart Rate</i>			
C. 6½ hours } Average 6 hr.		A. 6 hours from 90 to 82			
D. 6 hours } 15 min.		B. 6 hours from 78 to 78			
<i>Patients With Congestive Failure</i>		Maximum pulse reduction determined at one-hour intervals during 24 hours.			
NO.	TIME	NO.	TIME	FROM	TO
1	13 hr.	1	12 hr.	156	74
2	13 hr. 20 min.	2	8 hr. 20 min.	110	90
3	12 hr. 30 min.	3	16 hr.	96	80
4	14 hr. 30 min.	4	16 hr. 10 min.	132§	78
5	13 hr.	5	9 hr.	90	80
6	14 hr. 30 min.	6	15 hr.	88	70
7	14 hr. 45 min.	7	12 hr.	110§	102
8	15 hr.	8	12 hr.	96	88
9	14 hr. 40 min.	9	8 hr. 30 min.	86	86
10	15 hr.	10	16 hr.	120	108
11	16 hr.	11	9 hr. 40 min.	110§	74
12	14 hr. 20 min.	12	12 hr. 15 min.	120§	70
13	13 hr. 40 min.	13	8 hr.	88	84
14	14 hr.	14	12 hr.	90	82
15	14 hr. 40 min.	15	9 hr.	110	96
16	15 hr. 20 min.	16	12 hr.	96	96
17	15 hr. 30 min.	17	9 hr. 20 min.	108	92
18	15 hr. 10 min.	18	12 hr. 40 min.	146§	110
19	15 hr. 30 min.	19	7 hr.	112§	80
20	14 hr. 40 min.	20	8 hr. 30 min.	110	76
Average time for maximum RS-T change = 14 hours 24 minutes		Average			
		108.7 85.8			

*First record obtained eight hours after administration.

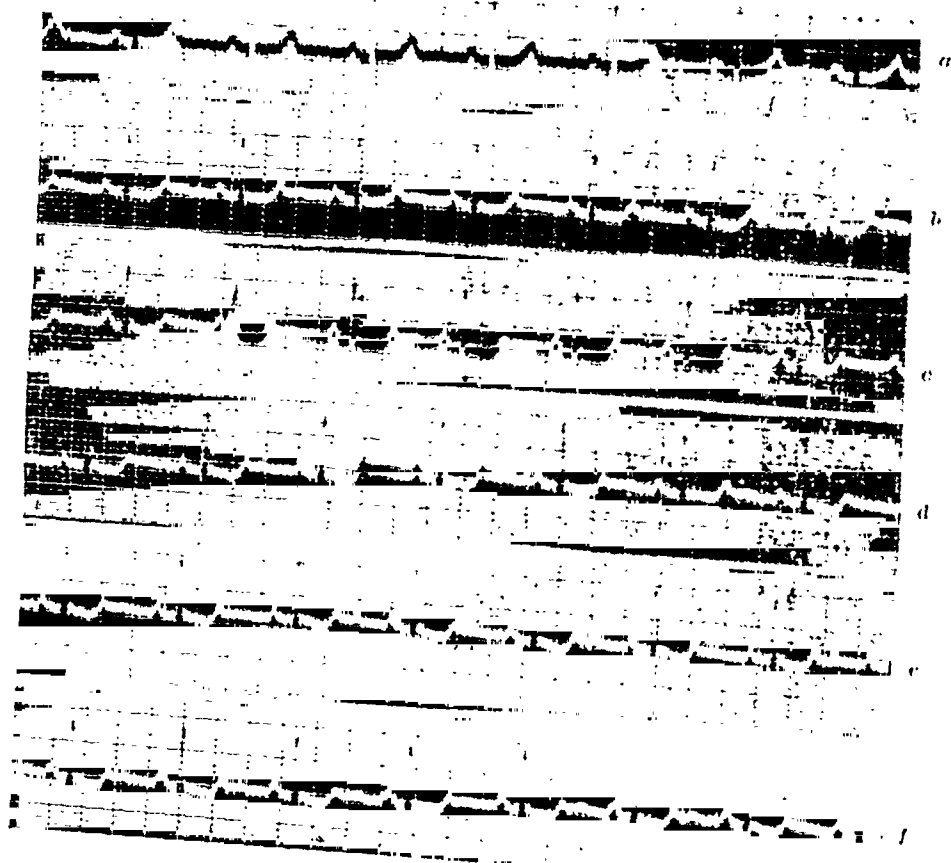
†Died pneumonia.

‡Died myocardial infarction.

§Patients with auricular fibrillation. R, normal sinus rhythm re-established.



A.



B.

Fig. 1.—Effect of lanatoside C, intravenously, on normal myocardium. A, Standard leads on normal prior to administration of lanatoside C—1.6 mg. B, Serial tracings taken in Lead 2. a, At time of injection of 8 c.c. of lanatoside C; b, fifteen minutes later; c, thirty minutes later; d, one hour twenty minutes later; e, one hour thirty minutes later; f, two hours later, digitals effect receding.

of observation there was no evidence of digitalis toxicity in these controls. The two normal persons who received digitalis purpurea leaf orally on a fasting stomach showed a maximal digitalis effect upon the RS-T segment in six hours and thirty minutes and six hours, respectively. Both suffered from extreme nausea which persisted for twelve to fourteen hours after medication. A digitalis effect upon the electrocardiogram of these two patients was first noted approximately four hours after the administration of the drug. It was noted that the RS-T segment returned approximately to normal within sixteen hours in the two patients who received lanatoside C, whereas in those who received the whole leaf orally, a segment change was in evidence for as long as forty-eight hours.

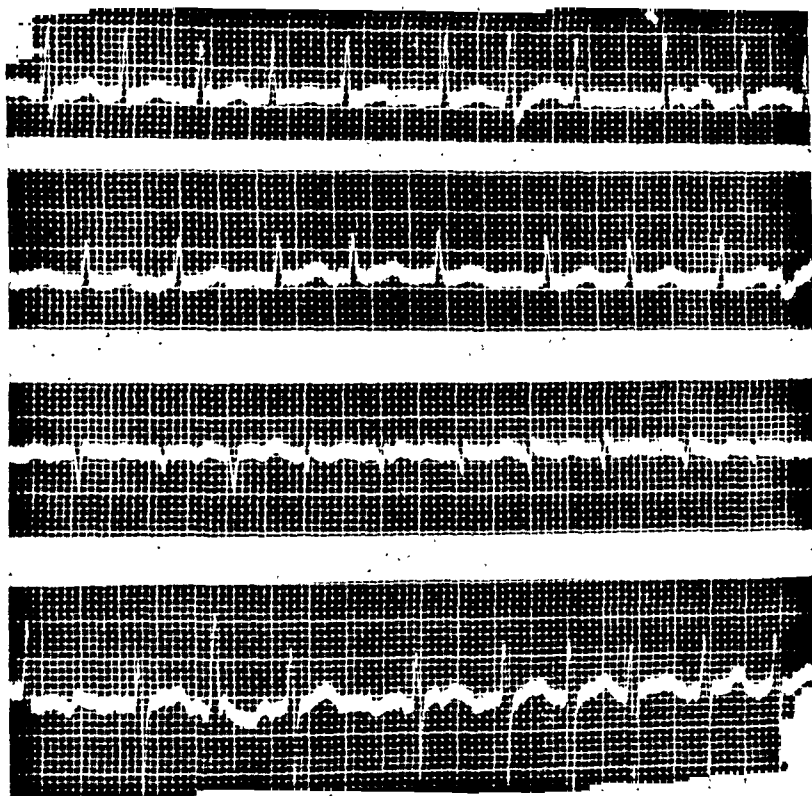


Fig. 2A.—J. L. A. Auricular fibrillation with rapid ventricular rate, ventricular premature beats, and left axis deviation.

Congestive Failure.—Of the twenty patients with congestive failure who received lanatoside C, two died during the study, one of lobar pneumonia, the other of myocardial infarction. Because of a psychosis in one case, it was impossible to repeat the tracings until eight hours after the administration of the drug. In this group the average time required for the maximal change in the RS-T segment was three hours and six and a half minutes. If the psychotic patient is excluded, the average time required for the maximal change in the RS-T segment was two hours and forty-five minutes. Only one of this group suffered from nausea. As was the case in Fahr's series, within three

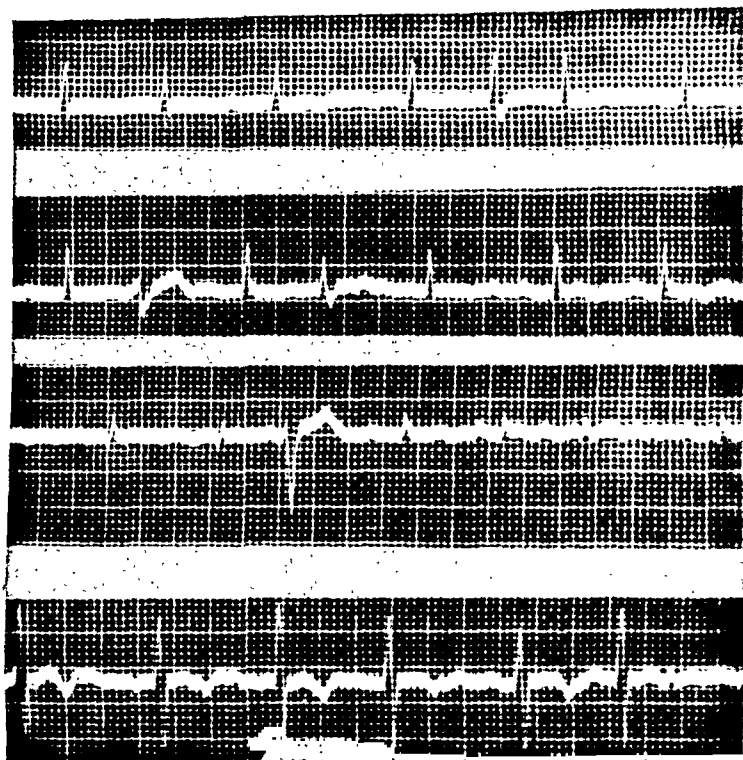


Fig. 2B.—J. L. A. Recorded twenty minutes after the intravenous administration of 1.6 mg. of lanatoside C. Definite digitalis effect, with appreciable slowing of the rate.

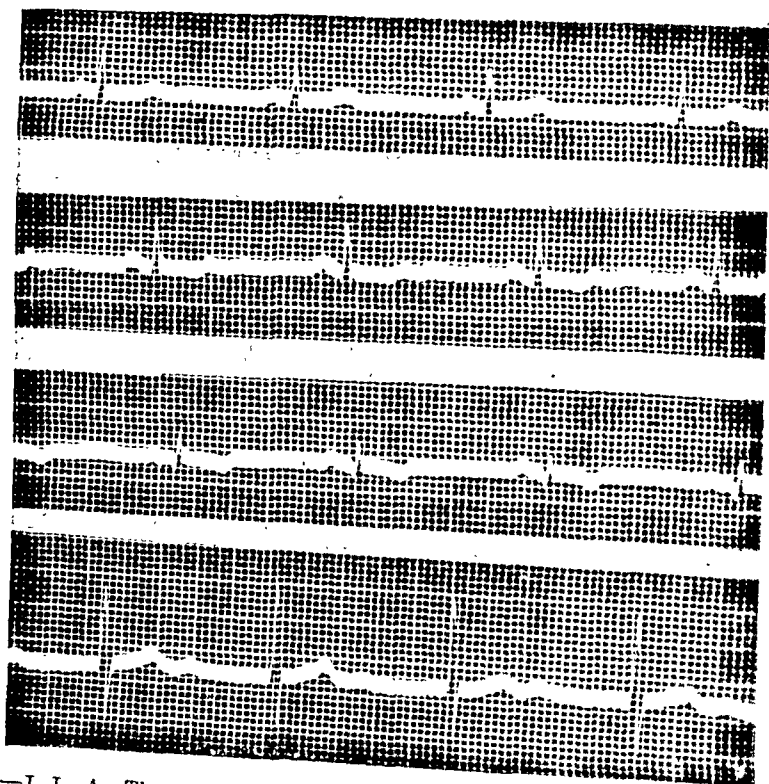


Fig. 2C.—J. L. A. Three hours after the administration of 1.6 mg. of lanatoside C. Normal sinus rhythm re-established, with definite slowing of the heart rate.

hours the average heart rate was reduced from 121 beats per minute to approximately 85. It was felt that at least part of this reduction in rate may have been a sinus effect. Inasmuch as frequent observations were made on the heart and pulse rate over this period, it is very unlikely that errors occurred. Of the surviving eighteen patients, all presented definite clinical evidence of improvement within a period of six hours. Nine patients of this group had auricular fibrillation. Of these, three recovered normal sinus rhythm within a period of twenty-four hours. Only one patient had a first degree block (A-V conduction time, 0.24 second) shortly after lanatoside C was given. Delay in A-V conduction appeared to be the exception rather than the rule in this series. One patient had slight nausea after the administration of lanatoside C. This nausea continued for a period of forty-eight hours.

In those with congestive failure who received digitalis purpurea orally, the average time required for a maximal change in the RS-T segment was approximately fourteen hours and twenty-four minutes. A digitalis effect on the RS-T segment was first noted eight and one-half hours after the drug was given. Eight of this group suffered from severe nausea and vomiting which were traceable specifically to the drug. There was an average reduction in the heart rate of approximately 30 beats per minute in the entire group within twenty-four hours after the administration of the whole leaf. Not unlike the group which received lanatoside C, a gradual clinical improvement was noted twenty-four hours later. The auricular fibrillation which was present in six cases in this group continued throughout the entire period of observation. The excretion of urine was increased equally in both groups. Because all of the patients in these groups continued to take digitalis after the study was discontinued, no return of the segments to normal was observed.

One patient who received lanatoside C presented an unusual clinical course which we were able to follow electrocardiographically, both prior to and after the administration of the drug. Because of the unusual circumstances, a brief summary of this case is given.

CASE REPORT

J. L. A., a white man 78 years of age, was admitted to the hospital on Jan. 28, 1941, complaining of vomiting, hiccough, insomnia, epigastric pain, and generalized weakness of seventy-two hours' duration. His past history was negative except for a surgical operation on his gall bladder four years prior to admission. At this time many stones were removed. Physical examination revealed a lean, elderly man, with no physical abnormalities other than epigastric tenderness. A tentative diagnosis of acute pancreatitis was made. Laboratory examination revealed a mild secondary anemia (hemoglobin, 70 per cent Sahli; erythrocyte count, 3,800,000; and polymorphonuclear leucocytes, 16,000). The urine was negative. On Feb. 9, 1941, while drinking a glass of milk, he was suddenly seized with a severe pain in the upper part of his abdomen. The temperature rose to 104° F., and extreme rigidity and tenderness were noted in the epigastrium;

roentgenologic examination revealed gas in the upper part of the abdomen, suggesting mild ileus. Soon after the appearance of these symptoms the patient's pulse rate became very rapid and irregular. Dyspnea made its appearance within a few hours, and was soon accompanied by moderate edema of the lungs and lower extremities. An electrocardiogram (Fig. 2A) disclosed auricular fibrillation with a rapid ventricular rate. While the temperature was still in the vicinity of 101° F., 1.6 mg. of lanatoside C were given intravenously because of the rapidly developing congestive failure; this was at 6 P.M. on February 17. Twenty minutes later there was a noticeable reduction in the pulse rate and heart rate (Fig. 2B), and at 9 P.M. the pulse rate was 70 and sinus rhythm had returned (Fig. 2C). At this time the electrocardiogram showed full digitalization. Laparotomy was performed at 10 P.M., and a diagnosis of peritonitis was made. Sinus rhythm continued throughout the entire operation. The patient had a stormy postoperative course, but his congestive failure continued to improve, and there was no reappearance of the auricular fibrillation.

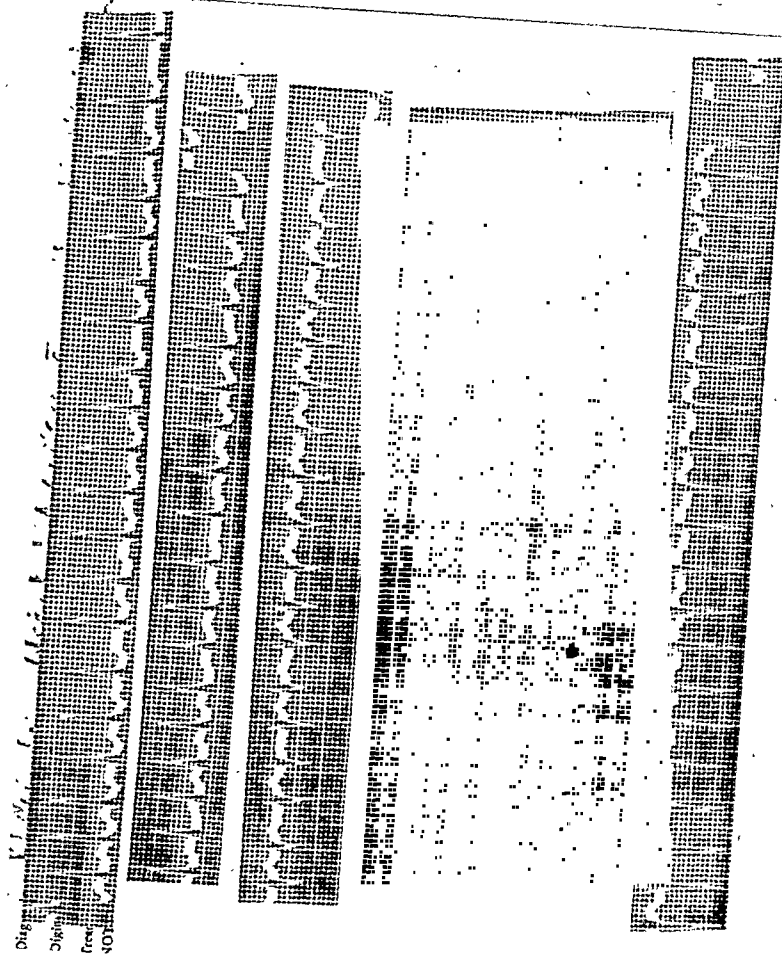
This case is reported because the desired therapeutic effect of digitalis was obtained during the course of acute congestive failure complicating a septic surgical condition. The presence of sepsis in no way inhibited the action of lanatoside C. Granting that the auricular fibrillation was paroxysmal and would possibly have terminated spontaneously, one is certainly led to believe that the drug proved its effectiveness.

DISCUSSION

The results obtained in this study from the intravenous administration of lanatoside C have shown that this drug exerts its maximal effect on the RS-T segment eleven to twelve hours sooner than a comparable dose of digitalis purpurea. If this criterion is acceptable, it should be of value in the treatment of congestive failure, especially since the segment changes are accompanied by clinical improvement in a like period of time. Although the material presented here is not large, and the results need further confirmation, encouraging evidence was obtained relative to the rapid action and low toxicity of this glucoside.

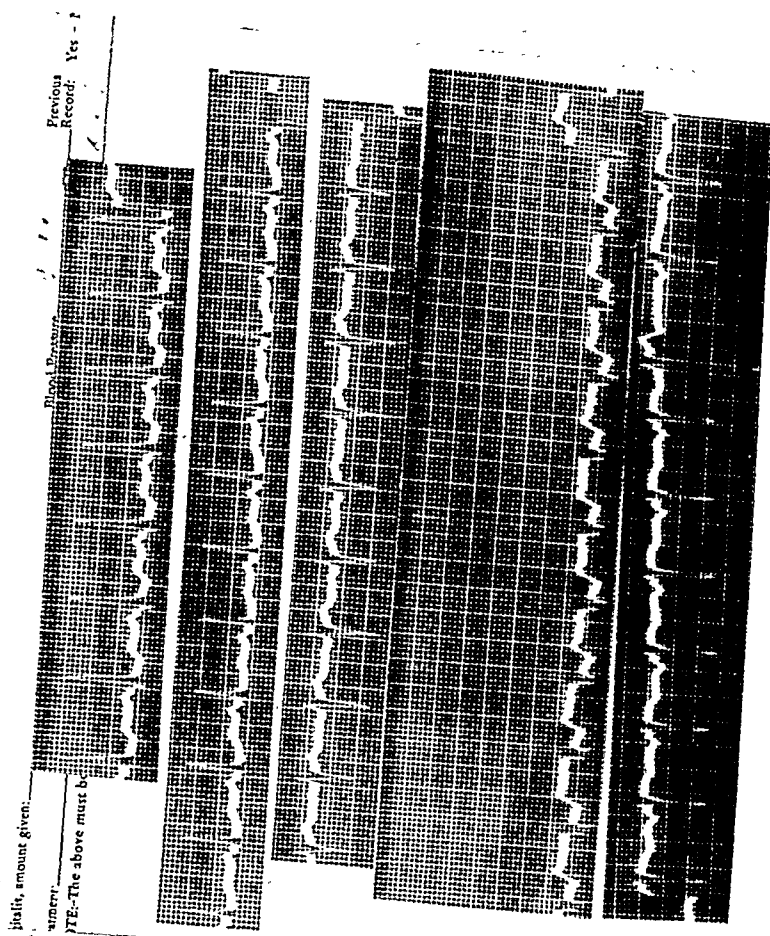
It is suggested that lanatoside C be given intravenously when the element of time is an important consideration in the treatment of congestive failure. This drug may also prove valuable for patients who are suffering from nausea and gastrointestinal disturbances when rapid digitalization is indicated. It is interesting that in the entire group of patients who received lanatoside C, the only side effect which could be attributed to its administration was nausea, and this was noted in only one case. On the other hand, nausea and vomiting occurred frequently after the oral administration of the digitalis leaf. Eight of the twenty patients with congestive failure suffered from these symptoms. Both of the control subjects, with no evidence of cardiac disease, developed severe nausea which was definitely traced to digitalis leaf. This observation leads one to believe that lanatoside C is comparatively free from the objectionable properties of the whole leaf.

It should be noted that of the eleven patients with auricular fibrillation, three regained normal sinus rhythm after the administration of



A.

Fig. 3.—A, Auricular fibrillation with rheumatic heart disease. Ventricular rate about 200 per minute. Quinidine failed to alter rhythm. B, 1.6 mg. of lanatoside C given intravenously at 10 A.M. Electrocardiogram taken at 10:30 A.M. Rhythm now normal. Left axis deviation. Possible changes in R-S-T segment caused by digitalis.



B.

lanatoside C (Fig. 3). The fact that this drug may aid in the re-establishment of normal sinus rhythm has been previously noted by many observers. Not a single patient with auricular fibrillation in the group in which digitalis purpurea was given by mouth regained normal rhythm throughout the entire period of observation.

With respect to maintenance of the digitalis effect, this study offers some interesting data. In the controls who received lanatoside C, the digitalis effect on the RS-T segment disappeared entirely within a period of sixteen hours, whereas this effect persisted for a period of forty-eight hours or more in the controls who received digitalis purpurea by mouth. It is clear that in order to retain the digitalis effect for a prolonged period of time, lanatoside C must be given intravenously at fairly frequent intervals, and it is therefore preferable to employ a digitalis preparation which contains all the glycosides for continued maintenance therapy. For those patients who do not require rapid digitalization or are not suffering from gastrointestinal disturbances, the preparations of digitalis now in common use are satisfactory.

SUMMARY AND CONCLUSIONS

1. The average time required for the development of maximal RS-T segment changes in the controls of this study after the administration of 1.6 mg. of lanatoside C intravenously was 27.5 minutes, as compared to six hours and fifteen minutes after giving 16 grains of digitalis purpurea by mouth.
2. In the presence of congestive failure, the intravenous administration of lanatoside C produced the maximal alteration of the RS-T segment within two to three hours, which was eleven to twelve hours sooner than when digitalis purpurea was given orally.
3. It seemed that the clinical manifestations of congestive failure disappeared with greater rapidity in the group of patients who received lanatoside C.
4. In the four controls the RS-T segment returned to normal in approximately sixteen hours after the administration of a single dose of 1.6 mg. of lanatoside C, and in approximately forty-eight hours after the administration of 16 grains of digitalis purpurea orally in a single dose.
5. These observations suggest that lanatoside C should be employed intravenously when rapid action is important in the treatment of congestive failure, or when gastrointestinal absorption of digitalis cannot be relied upon.
6. Unlike digitalis purpurea, lanatoside C does not produce untoward effects because it is more rapidly eliminated and seems to lack the nausea-producing elements of the whole leaf.
7. Our observations indicate that lanatoside C will prove to be a valuable drug in the treatment of congestive failure, especially when quick action is desired or when gastrointestinal symptoms are troublesome.

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UROLOGIC HYPERTENSION AS AN ENTITY

PAUL H. WOSIKA, M.D., PH.D., FREDERIC T. JUNG, PH.D., M.D., AND
CHAUNCEY C. MAHER, M.D.
CHICAGO, ILL.

THE studies to be reported in this paper were undertaken because of the occasionally striking cases we have observed¹ in which hypertension was found in the presence, not of Bright's disease, but of extrarenal disorders of the urinary tract. Since it is obviously fallacious to argue merely from occasional coincidences, we prepared, in 1939, a review² of the records of 600 private patients with persistent elevation of blood pressure. After taking out of this series the 26 cases (4.34 per cent) in which the hypertension could be accounted for by parenchymal renal disease (glomerulonephritis, Bright's disease, and other intrarenal or "medical" forms of kidney disease), we found a residue of 101 cases (16.8 per cent) in which the hypertension was concomitant with various types of urologic disease (various extrarenal or "surgical" forms of disease of the urinary tract).

These results were remarkable, because, although 4.34 per cent conformed to the figures given generally for the incidence of intrarenal disease among hypertensive patients, the incidence of extrarenal urologic disease was about four times as high. These urologic conditions included³ prostatic obstruction with or without complications in the upper urinary tract, 31 cases; chronic pyelonephritis with complications, 27; renal stone and complications, 18; prolapse of the uterus with hydronephrosis and infection, 7; diverticula of the bladder with complications, 5; urethral stricture (male), 4; cancer of the bladder with ureteral obstruction and infection, 2; renal tumors, 2; congenital cystic kidneys, 2; bladder stone, 1; congenital absence of kidney, 1; and vesicovaginal fistula, 1. Moreover, even this high figure, 101 cases, was conservative because many of the earlier cases lacked adequate urologic study. Pursuing this line of investigation further, we found,⁴ in a series of 97 patients with prolapse of the uterus, frequently associated with bilateral hydronephrosis and infection, that 74 (76 per cent) had hypertension. This percentage was distinctly higher than would be expected from other studies⁵ on the frequency of hypertension among hospitalized female patients in similar age groups.

During the progress of the investigation we found, in both the older and more recent literature, data which tended to confirm our suspicion that extrarenal lesions could cause hypertension. This suspicion is well

From the Department of Medicine, Illinois Masonic Hospital; the Department of Physiology and Pharmacology, Northwestern University Medical School; and the Department of Medicine, Cook County Hospital.

Received for publication March 17, 1942.

justified from the standpoint of experimental physiologic studies, which reveal the existence of nervous and humoral mechanisms that are quite adequate to explain such a relationship in terms of renal ischemia. But to confirm the suspicion clinically would require more than the isolated instances (Ritch, et al.⁶) in which hypertension and urologic disease have been found in the same patient.

Even when large numbers of such instances are available for study, the evidence may remain inconclusive. Thus, 113 patients (45 per cent of a series of 250 cases of essential hypertension) were found by Schroeder and Steele⁷ to have some form of organic renal disease. However, these authors state that many of these urologic conditions occur without hypertension, and vice versa: "Renal lesions associated with arterial hypertension have not been consistently found on postmortem examination, and the reason for this is unclear." Weiss and Parker⁸ have reported that hypertension often occurs in pyelonephritis, and they estimate that 15 to 20 per cent of the cases of malignant hypertension originate with pyelonephritis.

Hines and Lander⁹ found that urologic disease, regardless of type, had less influence on the incidence of hypertension than did a high normal blood pressure reading on the original visit, or a family history of hypertension. They conclude that "these data do seem to cast some doubt on the importance of renal disease in producing hypertension in the series as a whole and call attention to the importance of exercising caution in attributing a role of primary importance to a renal lesion simply because it is found in a patient who has hypertension."

Hypertension was present in 26.1 per cent of 180 patients with chronic bilateral pyelonephritis who were studied by Braasch and Jacobson;¹⁰ the incidence was 6 per cent higher than that in a control group. These authors also reported that 75 per cent of the patients with hypertension had systolic pressures below 180 mm. Hg, which constitutes a relatively benign elevation.

Williams and Harrison¹¹ found and classified 30 renal lesions among 100 subjects with increased blood pressure. Pearman, Thompson, and Allen¹² found 205 instances of renal disease among 500 cases of hypertension which were studied urographically. Admittedly, this was a select group, for 397 of the 500 patients had abnormalities in the urine that directed attention to the urinary tract. Further analysis showed that surgical disease of the kidney was no more common than would be expected for any other chronic medical condition. The conclusion was reached that the coexistence of renal disease and hypertension does not indicate a causal relationship. Horton¹³ reported that 40 per cent of 335 patients with hypernephroma had hypertension. Of 124 patients with other types of renal tumors, 57 had hypertension. In neither group was there a consistent alteration in blood pressure after removal of the tumor. This author concluded that the problem was not solved, even

though his study failed to substantiate the observations of others that the blood pressure fell after the removal of tumors. However, he admitted that, sporadically, some relationship seemed to exist.

Braasch, Walters, and Hammer¹⁴ found that the incidence of hypertension in a group of 1684 patients "subjected to renal surgical operation was no higher than it was in a group of patients taken at random." Hypertension was present in 46.5 per cent of 43 patients who were operated upon for primary, atrophic pyelonephritis. It was observed 161 times (20.3 per cent.) in 793 cases in which operation was performed for renal stone. These authors considered the role of infection to be most important.

Palmer, Chute, Crone, and Castleman¹⁵ found that 22 per cent of 212 patients with a persistent elevation of blood pressure had urinary tract defects, as shown urographically. These authors considered these lesions to "represent a participating or precipitating, rather than a major, factor."

If there is any association between urologic lesions and hypertension it should be ascertained. Obviously, a single instance of bilateral or unilateral ureteral obstruction and recurrent infection, associated with hypertension, does not prove an etiologic relationship. In fact, when two conditions are individually rather frequent, they must occur together occasionally by pure chance. For this reason, the collection of a large number of coincidences of this sort in itself proves nothing. Therefore, since laboratory investigation was seriously handicapped by the chronicity of the processes concerned, we had hoped that other workers who had large series of cases available would publish their results. Since, however, upon retrospect, we found many cases in our series² that should have had additional studies for more complete diagnosis, it occurred to us that others may have had the same difficulty. In other words, although it is easy to publish a list of conditions, either assumed to be causal, or suspected to be from the fact that they occasionally occur in cases of hypertension, it is quite another matter to state the percentage of incidence of these various associated conditions and draw conclusions from these percentages. Thus many classifications have appeared¹⁶ in the literature, culminating in the list of 47 associated conditions compiled by Page.¹⁷ It was decided, therefore, that a statistical analysis of the problem, using autopsy material, would be desirable.

MATERIAL AND METHODS

To avoid the use of biased data we examined the post-mortem protocols of the Department of Pathology of Northwestern University Medical School. These autopsies were performed in numerous general hospitals, and should represent a fair cross section of the autopsied population of a large city. One hospital limited admissions to men, so that there is a preponderance of males (69 per cent) in the series. The survey covered, without interruption, a 10-year period from 1930 to 1939, inclusive, so that any seasonal effect upon the sampling process was avoided.

TABLE I

Showing the number of males and females for each 10-year age group of 1962 patients.

AGE IN YEARS	SEX	
	MALE	FEMALE
20-29	77	61
30-39	97	87
40-49	236	119
50-59	328	128
60-69	343	120
70-79	239	67
80-89	39	18
90-99	3	0
Totals	1362	600
Per cent	69	31

Since we were interested in the effect of chronic disease, we excluded subjects whose age was 19 or under. The ages ranged between 20 and 99 years, although only 3 members of the group reached the tenth decade. We recorded the highest blood pressure measurement which was available, and used, as a dividing line between high and normal, 140 mm. Hg for the systolic, and 90 mm. Hg for the diastolic. It seemed to us that many instances of hypertension might not be included, for patients who died of cardiac failure, or in shock as a result of myocardial infarction, surgical procedures, accidents, etc., or in cachexia (carcinoma, tuberculosis, etc.) might show low measurements during their terminal illnesses. Therefore, we included the weight of the heart, for an increase in the size of the left ventricle in the absence of valvular disease constitutes one of the criteria by which elevation of the blood pressure may be diagnosed at autopsy. We considered the normal weights to be 300 grams for males and 250 grams for females.¹⁸ A $33\frac{1}{3}$ per cent increase¹⁹ in weight above these figures (400 grams for males and 333 grams for females) was regarded as evidence of hypertrophy. The presence or absence of valvular disease, etc., was carefully searched for and recorded. The term "urologic disease" was broad, including all the obstructions and infections or various combinations of these. In addition, gross congenital lesions (horseshoe kidney, renal aplasia, congenital cystic kidney, double pelvis with hydronephrosis) were incorporated. Small, occasional cysts were excluded, as were all the usual forms of nephritis and nephrosis.

The total number of records surveyed was 2,002. Not all were complete from our standpoint, and the unknowns were left out of the final computations. We attempted to include these unknowns by prorating and adding them proportionately to the known. We found, however, that if we included the unknowns and distributed them according to an arbitrary scheme we could prove any desired hypothesis. If we distributed them according to probabilities we obtained a diluting or attenuating effect. Therefore, by omitting all unknowns and uncertainties we felt that factual statements concerning the data could be made.

The otherwise difficult tabulation of these records was facilitated greatly by the use of punch cards and sorting machines. To obtain information concerning the significance of our observations, we employed the four-fold table and the chi-square test, as recommended by Pearl.²⁰

RESULTS

The results of the study have been arranged in four-fold tables, as illustrated in Table II. This is a summary of 1,179 patients. These were

TABLE 11

Four-fold table showing the presence or absence of urologic disease, compared with the systolic blood pressure. The figures in the small boxes in the upper left-hand corner of each cell represent the theoretical frequencies. The others are observed frequencies.

UROLOGIC DISEASE	SYSTOLIC BLOOD PRESSURE		TOTALS
	140 MM. HG OR OVER	139 MM. HG OR LESS	
Present	190 227	204 167	394
Absent	378 341	407 444	785
Totals	568	611	1179
Chi-square = 21.11		Probability = 0.000007 (Significant)	

subdivided into two groups: 568 were classified as hypertensive, with blood pressure readings 140 mm. Hg or over; 611 had 139 mm. Hg or less. Each of these groups was further subdivided as to the presence or absence of urologic disease.

In the hypertensive group, 227 patients, or 40.0 per cent, showed definite abnormalities of the urinary tract, and 341, or 60.0 per cent, at subsequent autopsy, showed no urinary tract disease. Of the 611 patients with systolic pressures below 139 mm. Hg, 167, or 27.4 per cent, had urologic lesions, and 444, or 72.6 per cent, showed no such lesions. If this group was typical, the chances are two in five that a patient with high blood pressure has urologic disease.

Significant conclusions may be drawn from this table, inasmuch as it shows the observed frequency of the two factors under consideration, i.e., urologic disease and hypertension. In other words, given 1,179 patients, of whom 394 have urologic lesions and 568 have hypertension, a simple probability calculation shows that, as a result of mere chance, 190 patients will have both. Thus $(394 \times 568) / 1179 = 190.0 =$ theoretical frequency. The data show, however, that 227 patients were observed to have both conditions. Therefore, $227 - 190 = 37 =$ the difference between the observed and theoretical frequencies. This means that there were 37 more people who had both hypertension and urologic disease than would be expected as a result of pure accident. This discrepancy between actual and theoretical frequency implies an association between hypertension and urologic disease. We confirmed this by the approved statistical procedure of the chi-square test which equals 21.11, which is large, and means that only 7 times in a million would so great a difference arise by accident. In other words, one may safely infer that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension.

Any attempt to make the association stronger by using high diastolic pressures alone, or in combination with elevated systolic pressures, failed. Also, adding enlargement of the heart to the criteria for hyper-

tension did not result in a greater correlation. The systolic blood pressure alone would seem to be an adequate criterion for hypertension in this connection. Our tabulations on this point will form the basis of a subsequent report.

It is generally accepted that some elevation of blood pressure is concomitant with increasing age. It is also generally agreed that the incidence of urologic disease is higher in older people. Our analyses of these two points in these autopsies bear out the truth of these fundamental concepts. The question is to ascertain whether the introduction of the age factor would significantly alter the basic relationship of urologic disease and high blood pressure.

We constructed Table III, a sixty-four-fold master-table, to enable a number of smaller table break-downs to be developed. This introduces age and sex factors, and permits the segregation of young males with and without urologic disease and/or hypertension from any other age group.

TABLE III

Shows a break-down of the data on 1210 patients into a sixty-four-fold table, comparing sex, blood pressure, and urologic disease by age.

SEX—SYSTOLIC BLOOD PRESSURE—UROLOGIC DISEASE									
AGE IN YEARS	MALE				FEMALE				TOTALS
	140 OR MORE		139 OR LESS		140 OR MORE		139 OR LESS		
	PRE	ABS	PRE	ABS	PRE	ABS	PRE	ABS	
20-29	6	10	6	25	1	9	5	20	82
30-39	3	15	2	30	3	18	10	25	106
40-49	19	46	18	60	8	22	10	34	217
50-59	41	63	27	87	21	26	12	26	303
60-69	47	65	29	68	12	25	8	27	281
70-79	50	34	36	31	12	11	3	12	189
80-89	9	2	3	6	3	3	2	3	31
90-99	0	0	1	0	0	0	0	0	1
Totals	175	235	122	307	60	114	50	147	1210

TABLE IV

Shows the presence or absence of urologic disease and hypertension among 458 males between the ages of 20 to 59 years.

MALES AGED 20 TO 59 YEARS				
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS	
	PRESENT	ABSENT		
140 mm. Hg or more	54	149	203	
	69	134		
139 mm. Hg or less	68	187	255	
	53	202		
Totals	122	336	458	
Chi-square = 10.188		Probability = 0.0014 (Significant)		

Table IV shows that, of 458 males between the ages of 20 and 59 years, 69 had both urologic disease and hypertension. Theoretically, only 54 should have been found. Further, there were more persons with normal

blood pressures and no urologic disease than was theoretically possible. Chi-square equals 10.18, and the probability equals 0.0014. This is significant, and means that only 14 times in 10,000 would this relationship occur as the result of chance.

TABLE V

Shows the presence or absence of urologic disease and hypertension among 381 males between the ages of 60 and 99 years.

MALES AGED 60 TO 99 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	95 106	112 101	207
139 mm. Hg. or less	80 69	94 105	174
Totals	175	206	381
Chi-square = 5.154		Probability = 0.0232 (Significant)	

Among 381 males from 60 to 99 years (Table V), 106 were observed to have urologic lesions and hypertension, which are eleven in excess of the calculated number. Chi-square equals 5.15, and the probability is 0.0232, which is significant.

TABLE VI

Shows the presence or absence of urologic disease and hypertension among 250 females between the ages of 20 and 59 years.

FEMALES AGED 20 TO 59 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	30 33	78 75	108
139 mm. Hg or less	40 37	102 105	142
Totals	70	180	250
Chi-square = 0.728		Probability = 0.3953 (Insignificant)	

There were 250 female patients between 20 and 59 years of age in the group (see Table VI). Here there was an excess of three persons who were observed to have urologic lesions and hypertension. Chi-square equals 0.728, and the probability is 0.3953, which is considered insignificant statistically. Of 121 females between 60 and 99 years of age (see Table VII), 27 were observed to have urologic disease, whereas 22 was the theoretically possible number. Chi-square equals 3.769, and, from a statistical standpoint, the probability rests upon the borderline of significance, at 0.0524.

Table VIII includes 97 males between 20 and 39 years of age. Nine were observed to have hypertension and urologic disease, whereas the

TABLE VII

Shows the presence or absence of urologic disease and hypertension among 121 females between the ages of 60 and 99 years.

FEMALES AGED 60 TO 99 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	22	44	66
	27	39	
139 mm. Hg or less	18	37	55
	13	42	
Totals	40	81	121
Chi-square = 3.769		Probability = 0.0524 (Insignificant)	

TABLE VIII

Shows the presence or absence of urologic disease and hypertension among 97 males between the ages of 20 to 39.

MALES AGED 20 TO 39 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	6	28	34
	9	25	
139 mm. Hg or less	11	52	63
	8	55	
Totals	17	80	97
Chi-square = 2.812		Probability = 0.0939 (Insignificant)	

expected number would be only six. Chi-square equals 2.812, and the probability equals 0.0939, which is significant.

In spite of the fact that the most significant associations occurred in male patients, it is noteworthy that in every group, whether male or female, young or old, the number of patients who had the combination exceeded the theoretical expectation. We feel that this is significant from a practical standpoint.

DISCUSSION

The purpose of this report is to answer the question whether or not urologic hypertension exists as an entity. "Organic" and "renal" hypertension have been suggested as alternative names for this condition. The word "organic" would include any demonstrable pathologic change which might cause hypertension (i.e., adrenal tumors, etc.) unless strict limitations were recognized and applied. The term "renal" would include the usual forms of nephritis. The term "urologic" would seem to be preferable because the lesions are definitely associated with the urinary tract; not entirely medical, nor yet entirely surgical, they result from infection, obstruction, or a combination of both.

To answer this question we studied 2,002 autopsy records on persons who were 20 or more years old. In the preceding statements the ref-

erence is, however, generally to less than 2,002 cases, because, in each table, before summarizing, we eliminated those cases in which a condition was not specifically stated to be either present or absent, and also those cases in which the blood pressure was not given in figures.

The results show that 40.0 per cent of patients with hypertension had urologic disease. This figure is higher than the estimated 30.0 per cent in our earlier studies. This means that 60.0 per cent of the hypertensive group had no evidence of urologic disease at autopsy. This large number has been noted by others, and has led some authors to assume that there is an unknown sensitizing mechanism for hypertension, which is set off only in certain susceptible people by the urologic disease. On the other hand, only 27.4 per cent of persons with no increase in blood pressure had urologic disease. This is difficult to explain, and is the reason for numerous statements that the relationship under consideration is incidental rather than causal.

However, since 37 more cases were observed than there should have been theoretically, and since this number was shown to be significant, it may be stated that there is a positive correlation between urologic disease and hypertension that is convincing statistically. The large size of the sample makes it extremely unlikely that the differences could have been due to chance. In other words, it may be inferred that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension. Actually, limitations must be imposed, because all we have shown is that, out of 568 patients who died, were autopsied, and had blood pressures of 140 mm. Hg or over during life, 40 per cent showed anatomic evidence of urologic disease post mortem.

Any attempt to make the association stronger by using high diastolic pressures alone, or in combination with elevated systolic pressures, failed. Also, adding enlargement of the heart to the hypertensive group did not result in a greater correlation. Using two criteria complicated the situation and did not increase the predictable number of patients who would be found to have urologic disease. The systolic blood pressure seems to be an adequate criterion for hypertension. Including the diastolic pressure and/or cardiac hypertrophy is not only impractical clinically, but it obscures the logic, complicates the mathematics, and attenuates the statistical correlation.

The master table (Table III) is included for completeness. Many comparisons are possible from this complicated sixty-four-fold table. For any age group of either males or females we may make comparisons between the simultaneous occurrence of urologic lesions and hypertension. This was done in Tables IV, V, VI, VII, and VIII only with male patients who showed statistically significant associations. Still there were always more persons who had both urologic disease and hypertension than would be expected theoretically.

Therefore, it may be stated that urologic disease, as we have defined it, is more common in patients with hypertension than is to be expected as a result of mere chance. The combination is rather more frequent than the isolated case reports would suggest, and this would indicate that urologic hypertension exists as an entity.

In this cross section of the autopsied population of a large city there is the additional factor that many of these persons had not run the complete life cycle of the disease. If our interpretation is correct, namely, that the development of urologic hypertension is a slow process which depends upon many factors related to abnormal kidney physiology, undoubtedly many of the patients died from other causes before the hypertension could be demonstrated.

All types of urologic disease should be thoroughly investigated and treated in their incipiency, if for no other reason than to avoid the possible development of hypertension. In addition, all patients with hypertension should be investigated for urologic disease, even if, by the time hypertension is present, the urologic lesions as well as the hypertension may be irremediable.

SUMMARY

1. A survey of 2,002 autopsy records was made to ascertain the relationship between urologic lesions and hypertension.

2. Statistical methods show that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension.

We wish to express our appreciation to Dr. J. P. Simonds, who permitted us to study the records of the Department of Pathology, and to Mr. Kenneth W. Revell, of the Regional Tabulating Unit, Division of the U. S. Public Health Service, for Tabulating the results.

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EVALUATION OF HEART SIZE MEASUREMENTS

HARRY E. UNGERLEIDER, M.D., AND RICHARD GUBNER, M.D.
NEW YORK, N. Y.

DIAGNOSTIC study of the heart seeks to ascertain whether heart disease is present, and, if so, to establish its etiology and severity. It is an aphorism that an enlarged heart is an abnormal heart, and, beyond indicating the presence of disease, the recognition of enlargement provides valuable information as to the type and the extent of the lesion, for characteristic changes frequently occur in various types of heart disease. Accurate estimation of the size of the heart, therefore, is most important. Methods for studying the size of the heart include physical examination, techniques employing the roentgen ray, and the electrocardiograph. The x-ray and the electrocardiograph are precision methods, but it does not follow, as is frequently assumed, that the information they convey is, therefore, necessarily exact. For the proper interpretation of roentgenograms and electrocardiograms, a knowledge of valid criteria for evaluating the size of the heart is essential, as well as an appreciation of certain physiologic and technical considerations.

PHYSICAL EXAMINATION

Recourse to the more specialized techniques is not always feasible, and careful physical examination usually enables one to make an approximate estimate of the size of the heart. It should be recognized, however, that there are serious limitations to inspection, palpation, and percussion, particularly when the chest wall is very muscular or obese, or in the presence of pendulous breasts or emphysema. When the apical impulse is palpable, the size of the left ventricle may be estimated from the relation of the leftmost point at which a definite forward lift is felt⁴ to a perpendicular dropped from the midpoint of the clavicle. The left nipple line is less dependable as a reference point because its position is variable; it may be situated well outside the midclavicular line in sthenic and obese male subjects, as well as in females. The left ventricle enlarges downward as well as to the left, particularly when aortic insufficiency is present, and may extend to the sixth intercostal space and yet remain well within the midclavicular line. Enlargement of the cardiac chambers other than the left ventricle cannot be detected on physical examination except in advanced stages. The right ventricle forms the anterior surface and lower anterior border of the heart, and, when enlarged, extends directly forward. Increased dullness to percus-

⁴From the Diagnostic Laboratory, The Equitable Life Assurance Society of the United States.

Received for publication Feb. 26, 1942.

sion in the third left intercostal space and over the sternum at this level is suggestive of enlargement of the conus of the right ventricle. This portion enlarges somewhat earlier than the body of the right ventricle. Enlargement of the right ventricle may be evidenced by an accentuated epigastric pulsation, i.e., retraction of the upper epigastrium during systole. This must be interpreted with caution, however, for the epigastric pulsation may be prominent normally in subjects of thin build or when the heart is overactive.

The right border of the heart is formed by the right auricle, and dullness to percussion which extends definitely beyond the right sternal border suggests enlargement of this chamber. The area of cardiac dullness may extend to the right of the sternum, however, as a result of displacement of the right auricle by enlargement of the other cardiac chambers, or because of pericardial effusion, so that this sign is not specific of right auricular enlargement. Nevertheless, enlargement of the right auricle may be considered to be present when, in addition to increased dullness beyond the right sternal border, there are peripheral signs of congestion, such as hepatomegaly and increased venous pressure. In the presence of pericardial effusion the right cardiac contour may be distinguished by means of an overpenetrated roentgenogram made a few seconds after an intravenous injection of diodrast, which outlines the right auricle within the pericardial effusion. Even the left atrium may form the right border of the heart when it is markedly enlarged, and, in cases of giant left auricle, comes to occupy the greater part of the right lower thoracic cavity. This is apparent not only on percussion, but frequently as a visible and palpable systolic heave of the right anterior chest wall caused by systolic distention of the massive atrium as a result of the free mitral regurgitation which is usually present. Lesser degrees of enlargement of the left atrium cannot be detected by physical examination, for this chamber extends posteriorly in the earlier stages of enlargement. Straightening of the upper part of the left border of the heart, although a relatively early sign of left auricular enlargement, as well as an indication of right ventricular enlargement, cannot be reliably discerned by physical examination.

ROENTGENOLOGIC METHODS

Less stress is placed on the estimation of the size of the heart by physical examination than formerly, for roentgenologic methods directly visualize the cardiac silhouette and permit detailed study of the size, shape, and position of the heart. Fluoroscopy, technically the simplest of the roentgenologic procedures, as well as the most generally available, provides the greatest information, and should be carried out routinely as a preliminary to further roentgenologic study. In any study of the size of the heart an attempt should be made to describe enlargement in terms of the individual chambers, for characteristic changes occur in

various types of heart disease. For this purpose fluoroscopy is of particular advantage because the contours of the separate chambers may be inspected in their entirety by rotating the subject into oblique positions, and their limits ascertained by observation of the pulsations. Adequate visualization of all the chambers is afforded by making roentgenograms in the posteroanterior, left anterior oblique (50° to 55°), and right anterior oblique (50° or over), or right lateral, position (Fig. 1). Examination in the latter view is aided by outlining (not filling!) the esophagus with a thick barium mixture, for the esophagus is in close relation to the posterior surface of the heart, particularly the left atrium.

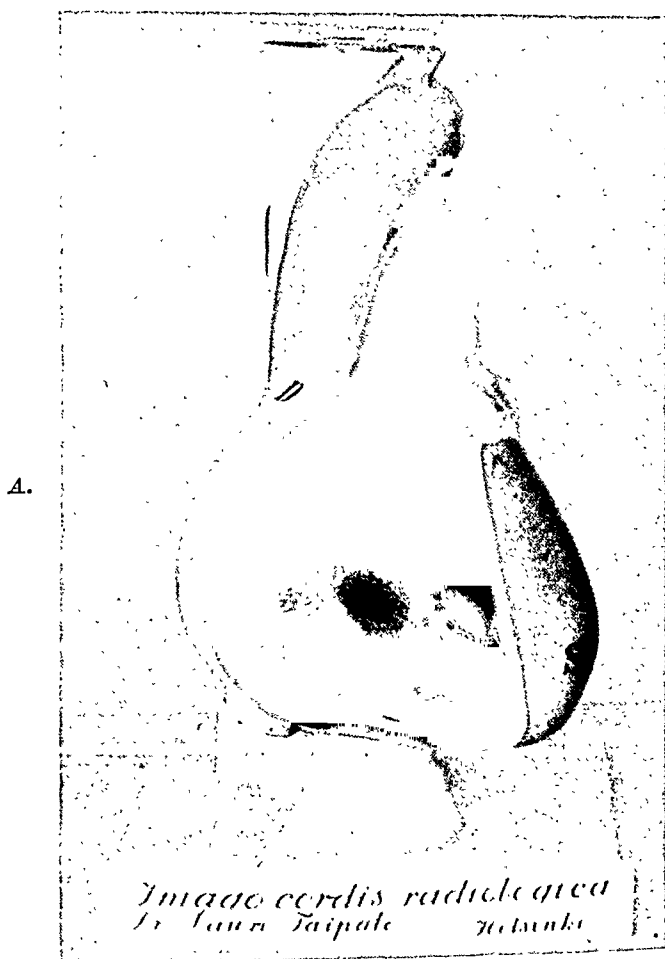
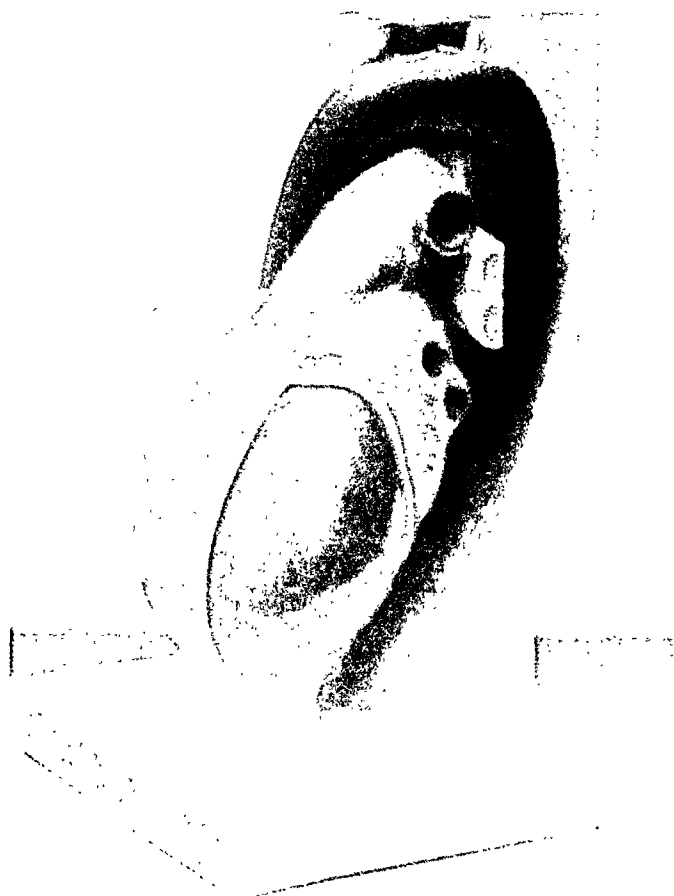


Fig. 1.—Positions for roentgenologic examination of the heart. A, Postero-anterior; B, left anterior oblique; C, right lateral.

The relation of the chambers of the heart to adjacent mediastinal structures, such as the esophagus, bronchi, and chest parietes, which can be ascertained by study in the oblique positions, is of great value in establishing whether or not enlargement is present. Thus, early enlargement of the left atrium is indicated by indentation and retrodisplacement of the esophagus, and also by upward extension of the left atrial contour toward the left main bronchus, which eventually becomes elevated and even compressed. The right ventricle forms the anterior sur-



B.



C.

face of the heart, and, when it is enlarged, extends forward toward the anterior chest wall, narrowing the precardiac space; this is revealed by study in oblique views.

Several measurements which purport to serve as criteria for enlargement of the individual heart chambers have been proposed.⁵⁻⁷ Attempts to measure the size of the cardiac chambers separately are necessarily inexact, however, because only one border is visualized; the shadows of the various chambers merge to form the cardiac silhouette. Although the limits of the cardiac chambers may be recognized by the pulsations on fluoroscopic examination, they cannot be clearly distinguished in roentgenograms, and the applicability of such measurements is, therefore, greatly limited.

Measurements are of greater value as an index of generalized enlargement of the heart than in estimating the size of the individual chambers, and there is a definite field of usefulness for measurement standards in evaluating enlargement of the heart as a whole. Frequently, enlargement of the heart does not involve individual chambers distinctly, and one can state only that the heart is enlarged. Mensuration is unnecessary when gross enlargement exists, but lesser degrees of enlargement often escape detection on inspection. Conversely, an apparently large cardiac shadow may assume less significance when it is considered in relation to body build. If proper account is taken of the physiologic variables which influence the size of the heart, mensuration is a valuable aid in ascertaining whether the heart is enlarged. Measurements are valueless, of course, when the position and configuration of the heart are distorted by an unusually high position of the diaphragm or skeletal abnormalities of the thorax, such as scoliosis or funnel chest.

Most measurements refer to the frontal cardiac silhouette. It is important that the subject be centered properly, which can be recognized in the roentgenogram by equidistance of the inner borders of the clavicles from the midpoint of the vertebral column. The exposure should be made in the erect or sitting position, and with respiration suspended at ordinary inspiration, for extremes of respiration or straining may cause marked variations in the size of the heart. To minimize projection distortion, roentgenograms should be made at a 2-meter tube film distance (teleroentgenography). Fluoroscopy is not well suited for absolute measurement of the size of the heart, except when the orthodiagraphic technique is employed, for there is considerable magnification of the heart image caused by divergence of the x-ray beam as a result of the short tube film distance which is usually employed in fluoroscopic examination. Even at teleroentgenographic distance (200 cm.) there is a magnification, caused by projection distortion, of approximately 5 per cent; this does not increase appreciably until the tube film distance becomes less than 150 cm. When the tube film distance is shortened still further, as in fluoroscopy, the magnification may be estimated approximately, in subjects of normal build, as 1 per cent enlargement for

each 10 cm. less than 200 cm. The degree of magnification in the roentgenogram depends not only on the tube film distance, but also on the object film distance; and magnification is accordingly greater in subjects with deep chests, in whom the heart contours are further removed from the film, than in slender subjects and children.

TYPES OF MEASUREMENTS

Innumerable measurements have been proposed for the estimation of the size of the heart, and this has resulted in general confusion and skepticism about all measurements. Broadly, measurements of the heart are of three types: linear diameters, area of the frontal cardiac silhouette, and calculations of the heart volume. Three diameters, the transverse, longitudinal, and broad diameters, are best known, and these suffice for estimation of the size of the heart (Fig. 2), for not only have standards been established for them, but, in addition, the area of the cardiac silhouette and the heart volume may be calculated from these diameters with fair accuracy.

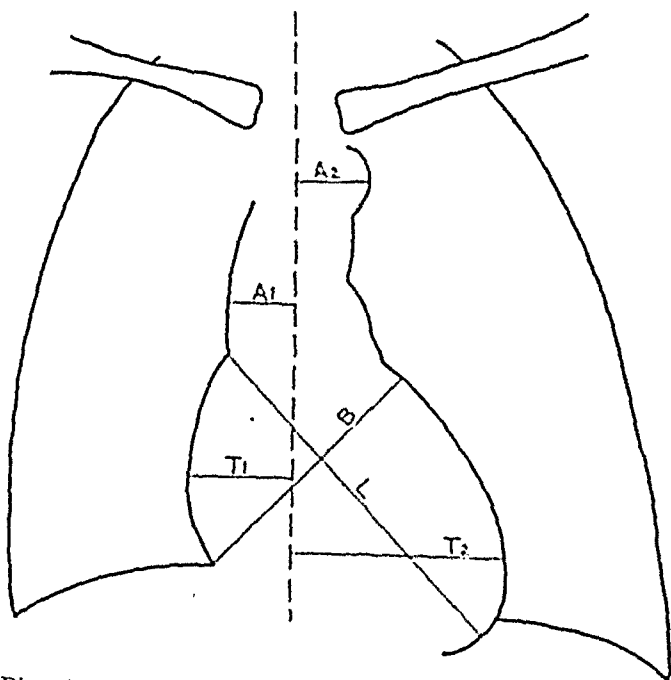


Fig. 2.—Diameters for measuring size of the heart: A_1 Plus A_2 , transverse diameter of aortic arch. T_1 Plus T_2 , transverse diameter. L , Long diameter. B , Broad diameter.

The simplest, most widely employed, and one of the most useful measurements is the transverse diameter, which is the sum of the greatest extension of the right border to the right, and of the left border to the left, of the midline. The cardiothoracic ratio, which is based on the assumption that the transverse diameter should be less than half the transverse diameter of the chest at the level of the diaphragm, has been widely popularized, but is crude and inexact. The width of the thorax is only a rough index of body stature, and is altered in any given case

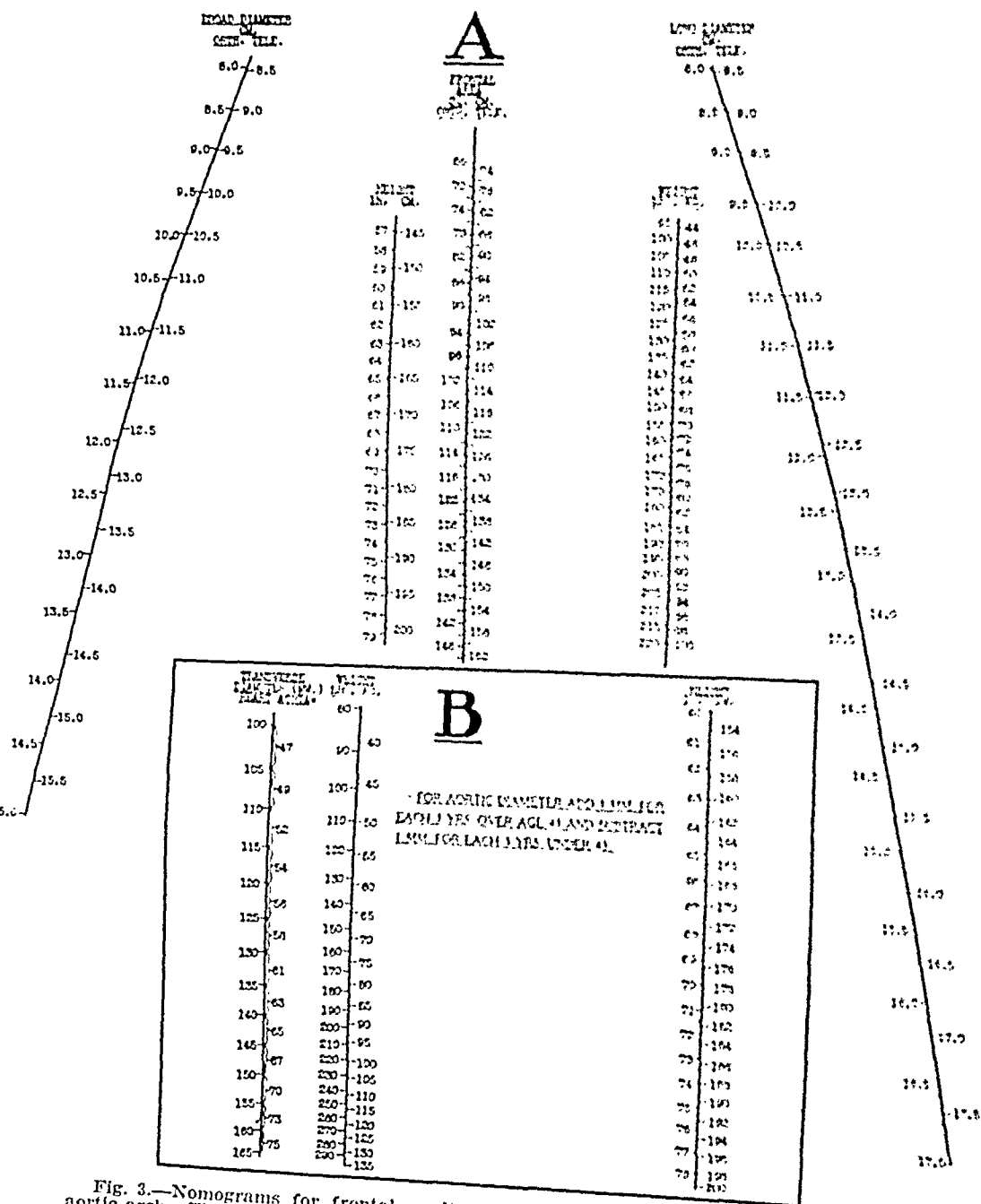
by respiration, and also in pathologic conditions, such as emphysema. Ordinarily the transverse diameter of the heart is considerably less than half the transverse diameter of the chest, so that appreciable enlargement may escape detection if this ratio is employed as an index of the size of the heart. More accurate standards, based on weight and height, have been established both for the orthodiagram⁸ and teleroentgenogram.² The influence of sex, and of age in adults, on the size of the heart is relatively small compared with the factors of weight and height, and, for practical purposes, may be disregarded in prediction standards. Teleroentgenographic standards are slightly greater than those for the orthodiagram, so that it is not proper to use the orthodiagram values in reading teleroentgenograms. Because of the increasing employment of the teleroentgenogram, a new prediction table, based on a study of 1,460 teleroentgenograms of normal subjects,² has been prepared, and this should be employed, rather than the older orthodiagram standards, when reading teleroentgenograms. A nomogram indicating the predicted transverse diameter from weight and height (Fig. 3) has been constructed.

The actual transverse diameter should not be interpreted too strictly in relation to the predicted value, for appreciable physiologic variations in the size of the cardiac shadow occur with respiration and changes from systole to diastole. Diameters which are more than 10 per cent above the predicted value should be regarded as abnormal, and the heart may be considered as almost certainly enlarged if the transverse diameter is over 15 per cent in excess of the predicted diameter. In measuring the transverse diameter, it is important to avoid including the extrapericardial fat pad which is frequently present, and which may merge with the lower portion of the left border of the heart. An increase in the transverse diameter is most often caused by enlargement of the left ventricle, but enlargement of any of the cardiac chambers, even of the left auricle, when it forms the right border of the heart, can widen the transverse diameter.

Two other diameters, the long and broad diameters, are well known, although these are somewhat less valuable individually than the transverse diameter. The long diameter extends from the junction of the cardiac and vascular silhouette on the upper part of the right border of the heart obliquely downward to the apex on the left. This diameter, which is approximately 10 per cent greater than the transverse diameter, is increased chiefly as a result of left ventricular enlargement. The broad diameter is the greatest diameter perpendicular to the long diameter. As a rule, it extends from the upper limit of the left ventricular contour to the lowermost point of the right border of the heart, but when the heart is of unusual configuration, the sum of the two greatest perpendicular extensions to the right and left from the long diameter is employed. If the heart is placed transversely, it may be necessary to extend the lower part of the right border slightly below the diaphragm

Nomograms for Area and Transverse Diameter of frontal heart silhouette

- A. PREDICTED AREA FROM WEIGHT AND HEIGHT¹ AND ACTUAL AREA FROM LONG AND BROAD DIAMETERS
 ($A = \frac{\pi}{4} L \times B$); FOR ORTHODIAGRAM AND TELEOROENTGENOGRAM.
 B. TRANSVERSE DIAMETER OF HEART² AND AORTIC SILHOUETTE³ PREDICTED FROM WEIGHT AND HEIGHT
 FOR TELEOROENTGENOGRAM



in its natural curve in order to delineate the broad diameter. The broad diameter averages about 15 per cent less than the transverse diameter.

The long and the broad diameters are of interest, not so much by themselves, but for their product, which is an expression of the two-dimensional size of the cardiac shadow.⁹ The product of these two diameters, which has been termed the heart rectangle, has been recommended as an index of the size of the heart in relation to the product of the height and width of the thorax.¹⁰ This ratio is expressed as

$$\frac{\text{rectangle of heart (L} \times \text{B)}}{\text{rectangle of lung (H} \times \text{W)}}$$

Normally the ratio averages 23 per cent; it varies from 20 per cent in subjects of asthenic habitus to 26 per cent in those of stocky build. The heart is considered enlarged if the ratio exceeds 28 per cent. Although standards based on thoracic configuration are less accurate than those predicted from weight and height, this ratio is less open to criticism than the cardiothoracic ratio, in which only the width of the chest is considered. When the weight and height are not available, as is frequently the case in hospital studies, the ratio, $\frac{\text{heart rectangle}}{\text{lung rectangle}}$ is a suitable method for evaluating the size of the heart.

An even simpler criterion, which is very satisfactory, is the relation of the lower part of the left border of the heart to a line dropped from the midpoint of the clavicle. Extension of the left border outside the left midclavicular line is usually indicative of left ventricular enlargement, and does not reveal changes in the other cardiac chambers, but it is the left ventricle which is most frequently enlarged in heart disease. This criterion has long been employed in physical examination, but serves equally well in roentgenologic study.²⁷

CARDIAC AREA AND VOLUME

The area of the frontal cardiac silhouette in relation to standards based on weight and height has been widely recommended as an excellent criterion of the size of the heart.^{1, 11, 12} In order to ascertain the area of the frontal silhouette, the upper and lower limits of the heart shadow must be completed by arbitrary and imaginary lines, and this requires considerable experience to attain duplicable results. The area is measured by means of a planimeter, or by counting squares within the area on cross-section paper. In orthodiagraphic examination, observation of the pulsations helps in outlining the contours. In the teleroentgenogram, however, the error in completing the upper and lower borders is much greater, and, for this reason, satisfactory frontal area measurements have not been obtained from the teleroentgenogram, although this method yields excellent results in orthodiagraphy in the hands of those who are well trained in the technique. Inasmuch as the cardiac shadow is ellipsoid in shape, its area may be calculated from

the product of its axial long and broad diameters (area of ellipse = $\frac{\pi}{4}$ long \times broad diameters.)⁹ Calculation of the cardiac area by means of the formula, $\frac{\pi}{4}$ long \times broad diameters, yields values which correspond very closely to the actual area, as measured by planimetry.^{13, 14} This product may, therefore, be used to estimate the cardiac area in lieu of planimetry. This is of particular advantage in the teleroentgenogram because the long and broad diameters can be measured accurately, whereas the planimetric estimation of the cardiac area is less accurate. The product, $2/3$ long \times transverse diameters, approximates the cardiac area, but is less satisfactory than the product of long and broad diameters, for the mean deviation from actual areas, as ascertained planimetrically in 134 orthodiagrams, was found to be 7 per cent, whereas with the long and broad diameter product the mean deviation in this group of 134 cases was less than 3 per cent. The predicted value for the cardiac area may be estimated approximately as follows: in a subject 5 feet 7 inches tall, weighing 150 pounds, the area should be 107 sq. cm. in the orthodiagram and 118 in the teleroentgenogram. One square centimeter is added for each 5 pounds over 150, and deducted for each 5 pounds under 150. Two square centimeters are added for each inch over 5 feet 7 inches, and deducted for each inch under 5 feet 7 inches. The actual cardiac area should not exceed 10 per cent over the predicted value, and, if it does, the heart may be considered as enlarged. A nomogram for prediction of the cardiac area from weight and height, and actual area as calculated from the long and broad diameters, are illustrated in Fig. 3.

The cardiac area is of great interest in another regard, in that it bears a close relation to the heart volume; the latter may be calculated from the cardiac area. In an extensive study on 62 cadavers, the area of the frontal cardiac silhouette was found to bear a close relation to the heart volume, and the formula, $V = 0.53A^{1.5}$, was proposed (where V = heart volume, A = area).¹⁵ More recently a modification of this formula, $V = 0.63A^{1.45}$, has been recommended;¹⁶ this yields values 6 per cent less than the older formula in the ordinary range of frontal area, varying from 90 to 130 sq. cm. Another formula for estimating heart volume from the frontal area is $V = 0.36$ long \times broad \times transverse diameters.*

*This is a modification of the Kahlstorf formula,¹⁸ which has been widely recommended, but which requires study in the lateral as well as the frontal position.

$V = 0.63 A \times T$, where V = heart volume

A = area of frontal silhouette

T = greatest horizontal anteroposterior diameter of the heart in the lateral position

The anteroposterior diameter of the heart may be estimated as 73 per cent of the frontal transverse diameter; in 150 cases it averaged 73 per cent, with a probable error of 6 per cent (calculated from data of Roesler, H. "The Relation of the Shape of the Heart to the Shape of the Chest," *Am. J. Roent.* 32: 464, 1934). Employing this ratio in place of the actual anteroposterior diameter, and the expression for cardiac area, ($A = \frac{\pi}{4}$ long \times broad diameters), the formula becomes $V = 0.36$ long \times broad \times transverse diameters. In 104 cases, chiefly normal subjects, the mean heart volume, as calculated by this formula, was 680 c.c., whereas the mean heart volume as calculated by the Bardeen formula was 687 c.c. The average deviation of these two formulas was 41 c.c.

Several other methods which take into account measurements in lateral or oblique positions, in addition to the frontal views, have been suggested.¹⁷⁻²¹ When the heart volume is estimated from teleroentgenograms, it is necessary first to correct the diameters for magnification (Fig. 3) before multiplying them to obtain the volume.

Although estimation of the heart volume is of great theoretical interest, the practical applicability is limited, particularly when study in more than one position is required. Apart from considerable variations in normal subjects, the volume varies from 25 to 30 per cent between systole and diastole, and the phase of the cycle must, therefore, be known. The volume during systole and diastole can be estimated by means of roentgenkymograms, but these are not generally available. The difference between the diastolic and systolic volumes, as measured kymographically, has been used to estimate cardiac output.^{22, 23} The ratio,

$$\frac{\text{diastolic heart volume}}{\text{stroke volume}},$$
 which ordinarily varies from 7 to 10, is a direct expression of the efficiency and functional state of the heart in accordance with Starling's Law. This ratio is of greater significance than the heart volume or stroke volume alone, and any considerable increase betokens impaired cardiac reserve.^{22, 24}

MEASUREMENT OF THE AORTA

Roentgenologic examination of the heart should invariably include the aorta, for abnormalities such as enlargement, tortuosity, and calcification occur very frequently in heart disease, particularly in hypertensive and arteriosclerotic heart disease and in syphilis. Measurement of the true caliber of the aorta is difficult because both contours are not visualized in the frontal position. The left border of the descending aortic arch is visualized in the frontal roentgenogram, and, if the esophagus is filled with barium, the right border of the aorta is indicated by the aortic indentation of the esophagus; therefore, the diameter at this level of the aorta can be ascertained.²⁵ The diameter of the transverse arch of the aorta can frequently be measured directly in the left anterior oblique position, particularly when some degree of emphysema is present to aid contrast, or when overpenetration technique is employed. These methods indicate the size of the transverse and descending aortic arch, but it is the ascending aorta which is most often enlarged in disease. The first portion of the ascending aorta is buried in the cardiac shadow, and cannot be studied by any means except contrast visualization with diodrast.²⁶ Enlargement of the ascending aorta is evidenced by prominence of the right border of the vascular pedicle, or by a forward bulge of the anterior border of the aorta, as observed in the left anterior oblique view. An increase in the transverse diameter of the vascular pedicle in the frontal roentgenogram does not specifically indicate enlargement of the aorta, for this may result from tortuosity alone; however, this measure-

ment is useful in that it does distinguish between a normal and abnormal aorta. In normal subjects the right border of the vascular pedicle is frequently formed by the superior vena cava, rather than the ascending aorta. In a recent study,³ it was found that the transverse aortic diameter in normal subjects is closely related to weight and height. The table established for predicting the transverse diameter of the heart from weight and height may be employed equally well for the aortic diameter (Fig. 3). A correction factor for age is necessary; 1 mm. is added for each three years over the age of 43, and subtracted for each three years under the age of 43. Deviations from the predicted value up to 10 per cent are within allowable normal limits, but deviations in excess of this are infrequently seen,* and the aorta may be considered as almost certainly abnormal if the diameter exceeds 15 per cent above the predicted value, for 92 per cent of normal subjects fall within this range.²⁷ Although height, in conjunction with weight, is an important factor in predicting the transverse diameter of the heart, whereas age is of little consequence, this is not so with the transverse diameter of the aortic arch. In an analysis of 372 teleroentgenograms of normal subjects, the authors found that the correction for height between 59 and 76 inches was less than 1 mm., and height may, therefore, be disregarded. A prediction formula for the teleroentgenographic aortic transverse diameter is given by the equation, aortic transverse diameter (mm.) = 0.30 age, plus 0.14 weight (pounds), plus 23.86. This gives approximately the same values as those obtained by consideration of height, weight, and age. The transverse diameter of the aortic arch is a simple and valuable standard for measurement of the aorta. It is important that the roentgenogram be made with the subject properly centered, for even slight rotation into oblique positions markedly alters the aortic transverse diameter. If the diameter is found to exceed normal values, further study in the left anterior oblique position is indicated, for the aortic arch is best visualized in this view.

ELECTROCARDIOGRAPHIC SIGNS OF ENLARGEMENT

It has long been recognized that characteristic electrocardiographic patterns occur with enlargement of the cardiac chambers, but this aspect of electrocardiography has received relatively little attention. It is not generally appreciated that the electrocardiogram provides the most sensitive method for detecting hypertrophy of the left ventricle. Considerable hypertrophy may exist without any enlargement of the left ventricular cavity, the so-called concentric hypertrophy. Since hypertrophy may be a matter of an increase in thickness of the myocardium of only a few millimeters, this cannot be discerned in the

In a series of 372 cases which were studied by the authors the actual aortic diameter was more than 10 per cent over the predicted in 17 per cent of normal subjects. Identical observations in a large series of cases were reported by H. H. Fellows, and also C. P. Clark (discussion of paper by Sheridan).

roentgenogram unless associated enlargement of the cavity is present. Concentric hypertrophy may be suggested, however, by increased convexity of the left ventricular curve, even though the dimensions are not measurably increased. Hypertrophy of the left ventricle is usually accompanied by left deviation of the electrical axis in the electrocardiogram. This alone is of no diagnostic value, however, for it occurs in a very large percentage of normal subjects, particularly those who are heavy-set and have transversely placed hearts. Indeed, one reason for the occurrence of left axis deviation in most cases of hypertension is that the greater number of subjects with hypertension are of sthenic build, in whom left axis deviation occurs normally. Left axis deviation, therefore, cannot be considered indicative of "left ventricular preponderance," a term which has been used ineptly as synonymous with left axis deviation. Marked left axis deviation, when the QRS complex is inverted in Lead II as well as in Lead III, does not occur normally, but is caused by myocardial involvement rather than ventricular enlargement. This type has been termed pathologic left axis deviation.

Although left axis deviation itself is no indication of left ventricular hypertrophy, patterns occur which are characteristic of hypertrophy when left axis deviation is associated with other changes in the ventricular complex. An increase in the voltage of the QRS complex in the standard limb leads, most often in Lead I, occurs quite regularly with left ventricular hypertrophy. In an analysis of the electrocardiograms of 460 normal subjects with left axis deviation,²⁷ the voltage of the QRS complex was less than 1.56 millivolts in 95 per cent of cases, and the sum of the R wave in Lead I and the S wave in Lead III was less than 2.21 millivolts. In 99 per cent the voltage was less than 1.77 millivolts, and the sum of the R wave in Lead I and S wave in Lead III was less than 2.54 millivolts. These values were exceeded, on the other hand, in a very large percentage of cases of left ventricular hypertrophy. The sum of the R wave in Lead I and the S wave in Lead III was found to provide a somewhat more sensitive criterion of hypertrophy than the voltage in any one lead alone.

Characteristic changes occur, too, in the terminal deflections of the ventricular complex, and these may occasionally precede the increase in voltage. In Lead I the S-T segment becomes displaced below the isoelectric line, and there is a reciprocal elevation of the S-T segment in Lead III. In advanced stages the S-T segment may be depressed in Lead II, as well as in Lead I. It is generally stated that depression of the S-T segment is significant if it is more than 1 mm., but depression of any noticeable degree (0.5 mm.) in Lead I in association with left axis deviation must be considered significant because this was never observed in the series of 460 normal subjects with left axis deviation who were studied by the authors.

Flattening and subsequent inversion of the T wave in Lead I occur with left ventricular hypertrophy, and, in more advanced stages, inversion of the T wave occurs in Lead II, as well. There is a reciprocal relationship between the T wave in Leads I and III; as the T wave becomes deeply inverted in Lead I, it becomes more upright in Lead III. Normally, the T wave in Lead I should be at least 1 mm. in amplitude, and low amplitude in association with left axis deviation is suggestive of left ventricular hypertrophy.

It should be noted that the S-T segment and T-wave changes just described may be present with left ventricular hypertrophy in the absence of left axis deviation.^{27, 28} This is particularly likely to occur in subjects of slender build. The changes in the S-T segment and T wave, although they are characteristic, are less specific for left ventricular hypertrophy than increased voltage, for they may occur in a variety of other conditions. In the more advanced stages of left ventricular enlargement, slurring, notching, and widening of the QRS complex are observed, and eventually the pattern of left bundle branch block appears. This is quite different in origin from the slight increase in the duration of QRS (up to 0.10 second) which may result from prolonged excitation of the ventricle caused by hypertrophy itself. It is most probably the result of the myocardial fibrosis which is generally associated with marked left ventricular enlargement, and which occurs chiefly in the subendocardial layers of the left ventricle and the interventricular septum, and therefore may involve the conduction system which ramifies in this region. In addition to the abnormalities described, changes in the precordial leads occur with both left ventricular hypertrophy and right ventricular hypertrophy.²⁹

A characteristic electrocardiographic pattern occurs with hypertrophy of the right, as well as of the left, ventricle. The changes consist of right axis deviation, accompanied by depression of the S-T segment in Lead III and frequently Lead II, and inversion of the T wave in Lead III, and eventually in Lead II, as well. The voltage of the QRS complex is not regularly increased as it is with left ventricular hypertrophy. When the pattern is fully developed it is quite characteristic of right ventricular hypertrophy, but frequently in the less advanced stages it may be difficult to be certain that right ventricular strain is present because similar changes may occur in normal subjects of slender build, or as a result of positional changes of the heart. The electrocardiographic abnormalities frequently disappear in asthenic subjects, however, when the tracing is made in the recumbent position.

Auricular enlargement, also, may be revealed in the electrocardiogram. The left auricle is the one which is usually enlarged, most often because of mitral stenosis. Changes occur in the P waves as a result of impaired conduction through the dilated and hypertrophied auricle. The P wave

becomes notched, its duration exceeds 0.10 second, and it increases in amplitude to more than 0.25 millivolt. Ultimately, auricular fibrillation ensues as a result of longstanding auricular enlargement. Auricular premature beats and auricular flutter occasionally presage the change to auricular fibrillation. Although hypertrophy of the left ventricle may be detected earlier in the electrocardiogram, roentgenologic methods are superior in revealing auricular and right ventricular enlargement. When generalized cardiac enlargement is present the electrocardiographic changes are less specific, and the opposite effects of right and left ventricular enlargement may balance each other so that there is no deviation of the electrical axis, although other abnormalities, such as increased voltage and changes in the S-T segment and T waves tend to persist. The electrocardiogram may be relatively normal when enlargement is caused by dilatation of the cardiac chambers rather than by hypertrophy. Roentgenograms, therefore, are superior when generalized enlargement exists.

SUMMARY

Accurate estimation of the size of the heart is important. So far as possible, an attempt should be made to define enlargement in terms of the individual chambers, for characteristic changes occur in various types of heart disease. Enlargement of the cardiac chambers other than the left ventricle cannot be detected on physical examination except in advanced stages. Fluoroscopic or roentgenographic examination in frontal and oblique positions is of greater advantage in evaluating enlargement because the contours of the separate chambers may be visualized.

If proper account is taken of the physiologic variables which influence the size of the heart, mensuration is of value in ascertaining whether the heart is enlarged. Measurements are of greater value as an index of generalized enlargement of the heart than in ascertaining the size of the individual chambers. There is a definite field of usefulness for measurement standards in evaluating the size of the heart as a whole, for frequently enlargement does not involve individual chambers distinctly, and one can state only that the heart is enlarged. Mensuration is unnecessary when gross enlargement exists, but lesser degrees of enlargement often escape detection on inspection. Conversely, an apparently large cardiac shadow may assume less significance when it is considered in relation to body build.

The most practicable measurements are the transverse diameter and the area of the frontal heart silhouette. Planimetric measurement of the cardiac area is difficult and inaccurate in the teleroentgenogram, but the area may be calculated with considerable accuracy from the product of the long and broad diameters. A nomogram which enables one to calculate the frontal area from the long and broad diameters is presented. Predicted values for the frontal area from weight and height are shown

on the same nomogram, and, in addition, the predicted transverse diameter of the heart and of the frontal aortic arch silhouette are included. These measurements, i.e., the frontal area, the transverse diameter of the heart, and the transverse diameter of frontal aortic arch silhouette suffice for evaluating the size of the heart. Employment of the nomograms permits the convenient application of these more valuable cardiac measurements. Measurements are not to be regarded as final, but should be employed to complement careful study of the individual cardiac chambers by fluoroscopic examination; and the diagnostic significance of cardiac enlargement should always be considered in relation to the associated clinical observations.

Characteristic electrocardiographic patterns are observed when there is enlargement of the various chambers, and it is emphasized that the electrocardiogram provides the most sensitive method for detecting hypertrophy of the left ventricle. Roentgenologic methods are superior in revealing auricular and right ventricular enlargement, or when generalized enlargement exists. The electrocardiographic changes are the result of hypertrophy, rather than enlargement as such. The electrocardiogram may be relatively normal when enlargement is the result of dilatation without associated hypertrophy.

The authors acknowledge with thanks the aid of Mr. R. A. Porter, of the Statistical Bureau of the Equitable Life Assurance Society, in the preparation of the nomograms for the area and transverse diameter of the frontal silhouette of the heart.

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A SIMPLE METHOD FOR MEASURING CARDIAC AREA FROM THE ORTHODIAGRAM

MILTON MAZER, M.D.

WASHINGTON, D. C.

THE size of the heart is important in the diagnosis of heart disease. Of the available methods of estimating it, all of which are necessarily indirect, the area of the frontal projection of the heart's roentgenographic shadow is one of the most useful. The area of such an orthodiagraphic tracing, with the superior and inferior borders drawn conjecturally, is usually measured by a planimeter, or by transferring the outline of the area to finely squared paper and counting the squares contained within it. The latter method, to be accurate, requires finely squared paper and an estimation of how much of the squares which are transected by the cardiac outline should be included. Hence, it is tedious. The planimeter, although it is accurate and convenient, is not always available. It seemed desirable, therefore, to investigate the possibilities of a method which would not require the use of a planimeter and would avoid the tediousness and potential errors inherent in the squared paper method.

In 1914, Nissim¹ described a simple method for measuring the frontal area of the heart's roentgenographic shadow. The outline was traced on a sheet of aluminum which was cut out and weighed. The weight of one square centimeter of the aluminum sheet was also ascertained. The appropriate calculation gave the frontal area of the heart. A partial application of this method, in which paper was used instead of aluminum, was utilized by Strong and Gordon² to ascertain the effect of strophanthin on the size of the rabbit's heart. They did not actually measure the cardiac area, but used the method only for comparative purposes. They noted that A. E. Cohn had previously employed the same procedure.

METHOD

The method for measuring the area of the orthodiagraphic tracing which is described in this paper is essentially a modification of those mentioned above. The steps are as follows: The outline of the heart, with the superior and inferior borders drawn in conjecturally, is retraced on a piece of the same tracing paper which is used for the original orthodiagram. A sharply pointed grade 4 pencil has been found satisfactory for this purpose. The traced area is then cut out with scissors. The cutout is weighed on a chemical balance and its weight recorded. On another piece

From the Cardiovascular Research Unit, Veterans Administration.

Published with permission of the Medical Director of the Veterans Administration, who assumes no responsibility for the opinion expressed or the conclusions drawn by the author.

Received for publication March 9, 1942.

of tracing paper a square, 10 cm. \times 10 cm. (100 sq. cm.), is drawn by means of a right-angled triangle and a centimeter rule. This area is cut out and weighed, and serves as a standard. Since the weight of 100 sq. cm. of the tracing paper and of the cutout which represents the cardiac area is known, the area of the cutout may be computed.

For example, the traced cutout of one orthodiagram weighed 362.5 mg. The average weight of 100 sq. cm. of the paper used in this study was 282.1 mg. One square centimeter of the paper, therefore, weighs 2.821 mg. Dividing the weight of the orthodiagraphic cutout by this factor gives a value of 129.2 sq. cm. for the area. Or, to put it in general terms,

$$\text{Area of cutout (sq. cm.)} = \frac{\text{Weight of cutout}}{\text{Weight of 1 sq. cm. of paper}}$$

Since the weight of the standard is a vital measurement which affects all estimations, it has been found desirable to ascertain the weight of an average standard from 10 to 12 separately measured squares. This value may be used in all subsequent estimations, but should be checked whenever a new roll of paper is employed.

Accuracy of Method.—The areas of 100 orthodiagraphic tracings and arbitrarily drawn areas of the shape of the heart were obtained by this method and checked by the planimeter. The average error for the 100 tracings was 2.8 per cent. The average negative error was 2.1 per cent; the average positive error, 3.2 per cent. Since the errors in the orthodiagraphic projection and tracing are greater than this, and since variations from normal of less than 10 per cent in cardiac area are not usually considered significant, it is apparent that this method is sufficiently accurate for all practical purposes.

Sources of Error.—The method has the following potential sources of error: (1) Variations in weight of paper; (2) errors in weighing; (3) errors in cutting outline; (4) errors in tracing.

An attempt was made to ascertain the magnitude of the variation in the weight of the tracing paper per unit area. Accordingly, 16 sheets of the paper were clipped together between sheets of thin cardboard with puncture clips. The tablet so formed was then cut into a roughly circular shape. By this means the errors caused by tracing and cutting the outlines were eliminated. The clips were then removed and the individual sheets weighed. The mean weight was 400.2 mg., with a standard deviation of ± 10.4 and an average deviation from the mean of 2.1 per cent. Therefore, variations in the weight of the tracing paper are quite small.

The errors in weighing, likewise, are negligible. The weight of the traced areas of paper was of the order of 250-450 mg. Hence, an error in weighing of 1 mg. would at most introduce an over-all error of only 0.4 per cent. Although in this study the method of swings was used in the weighings, this is probably not necessary in ordinary routine work. The sensitivity of the average chemical balance is such that balancing the pointer within 3 scale divisions of zero will never introduce an error greater than 0.5 per cent.

No method was devised for differentiating errors in tracing and in cutting of outlines. However, in order to ascertain the constancy of the method without recourse to planimetric control, 12 separate tracings of the same original area were made. The mean area was found to be 132.8 ± 3.4 sq. cm. The average deviation from the mean was 1.9 per cent.

The magnitude of the possible errors in tracing and cutting may be estimated from a consideration of the shape of the orthodiagram and the formulas which describe areas of such shape. In general, the shape of the frontal projection of the heart approximates an ellipse, and at times approaches a circle. If, in tracing and cutting a circle 100 sq. cm. in area, the circle is cut 1 mm. larger than the original along its entire circumference (making a 2 mm. error in the diameter), the error in area will be 3.5 per cent. Similarly, in tracing and cutting an ellipse 107.0 sq. cm. in area, positive errors in the radii of 0.9 mm. and 1.2 mm. will introduce an error of 3.7 per cent. Experience has shown that errors as great as these are not likely to be made.

The errors of this method were more often positive than negative. Of the hundred estimations, 65 showed positive errors, as compared with the planimeter, with an average error of 3.2 per cent, whereas 35 showed negative errors, with an average of 2.1 per cent.

The accuracy of the method was, in our hands, improved by practice. In the first fifty estimations the average error was 3.7 per cent, whereas in the last fifty it was 2.0 per cent.

SUMMARY

A simple method for measuring the area of the orthodiagraphic tracing is described. It requires no instruments which are not already available in the average hospital. The error of the method is quite small, and well within normal variations in the size of the heart and errors in orthodiagraphic projection and tracing.

I am indebted to Blanche B. Wilcox, Ph.D., for the planimetric measurements.

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AN INTERPRETATION OF THE INJURY AND THE ISCHEMIC
EFFECTS OF MYOCARDIAL INFARCTION IN ACCORDANCE
WITH THE LAWS WHICH DETERMINE THE FLOW OF
ELECTRIC CURRENTS IN HOMOGENEOUS VOLUME
CONDUCTORS, AND IN ACCORDANCE WITH
RELEVANT PATHOLOGIC CHANGES

ROBERT H. BAYLEY, M.D.
NEW ORLEANS, LA.

INTRODUCTION

CONSIDERABLE confusion and difference of opinion exist as to the interpretation to be placed upon the RS-T junction displacements caused by human and experimental myocardial infarction. For example, the prevalent idea that subepicardial damage produces an upward (positive) RS-T junction displacement and that subendocardial damage produces a downward (negative) RS-T junction displacement¹ is, in my opinion, clearly untenable. With certain reservations it may be admitted, in accordance with the opinion of others,² that the injury effects of infarction are brought about in essentially the same manner as those produced experimentally when the subepicardial region of the ventricular wall is damaged by heat, chemical agents, suction, or infection.

In the title of the present discussion the terms "injury" and "ischemic" refer to electrocardiographic effects, and have been defined in accordance with the membrane theory.²⁻⁵ The difference between an injured and an ischemic zone of cardiac muscle is one of function with respect to the electrical effects which are produced. In this regard, an injured zone is one which acts during diastole, and probably during systole, as the source of an electrical field of injury, and is a zone within which there exists or appears to exist a gradient in the intensity of polarization. The injured zone is responsible for the RS-T junction displacements which appear on the completed record only during systole.² An ischemic zone is one in which polarization is everywhere complete during diastole (as in the case of normal muscle), but (unlike normal muscle) is one in which the onset of polarization is abnormally tardy during the regression period.⁶ The existence of an ischemic zone of sufficient dimensions accounts for the primary T-wave changes which are occasionally observed before, and frequently after, myocardial infarction. Generally speaking, both an injured zone and an ischemic zone are regions which are deprived of their normal blood supply, and, therefore, both are ischemic, the former even more so than the latter. Nevertheless, it is of considerable importance from the electrocardiographic standpoint to differentiate the two zones in the manner described.

From the Department of Medicine of the Louisiana State University School of Medicine.

Received for publication, Feb. 26, 1942.

No demonstrable pathologic changes are implied by the ordinary use of the terms "injured zone" and "ischemic zone." As a matter of fact, local ventricular ischemia is known to be unattended by demonstrable structural change.⁶ It seems possible that an injured zone may likewise be unchanged in the ordinary pathologic sense. By the time a region of cardiac muscle has suffered sufficient damage to exhibit microscopic changes, the involved cells have, it appears, already become electrically inert. These statements simply agree with the idea that a large gap ordinarily exists between delicate changes in a physiologic process and demonstrable pathologic change.

ON THE INCOMPATIBILITY OF DIRECT AND INDIRECT MYOCARDIAL DAMAGE

The injury effects of subepicardial damage produced by heat, suction, infection, or chemical or mechanical agents are almost certainly the result of the electrical activity of a thin layer of injured cells which separates the dead from normal (or the damaged from normal) muscle.² The injured layer acts during diastole as if it were an electric double layer in which a uniformly distributed source resides at that surface directed toward normal muscle and in which a uniformly distributed sink resides at that surface directed toward dead muscle.² It may readily be shown⁷ by the laws which govern the flow of electric currents in volume conductors that the electrical field produced by an open double layer of the kind specified is proportionally represented by a single vector \hat{i} , the direction of which is that of a line drawn toward the center of the involved chamber normal to the plane circumscribed by the epicardial surface boundary of the double layer, and the magnitude of which is equal in units of length to the area of the plane in units of area. In recording the extremity leads (and unipolar leads), a current is introduced into the body-galvanometer circuit which neutralizes the effect during diastole of the diastolic field of injury.³ If accession is regarded as a partial reversal of polarization, let us say to one-half of the intensity of the resting state, then $2/3 \hat{i}$ is the effective electromotive force which is neutralized during diastole. Consequently, during systole, when the electrical field of injury again exists, with its polarity reversed, the neutralizing current is free to flow unopposed about the circuit, and the total effect on the completed record caused by injury is the same as if the field existed only during systole. That is, if the vector $2/3 \hat{i}$ describes the field of injury during diastole, a vector $-\hat{i}$ must describe the effect on the completed record during systole. The vector $-\hat{i}$ may be termed the spatial axis of injury. The projection of $-\hat{i}$ upon the frontal plane of the body gives the vector $-\hat{i}$, which may be termed the axis of injury.

Of considerable clinical usefulness, because of its simplicity, is the triaxial reference system (Fig. 1a) formed by translating the sides RL , RF , and LF of the Einthoven triangle in such a manner that their midpoints meet in a common point at the origin O . The reference axes

thus formed have a positive and a negative half, divided by the origin O . The reference axes divide the frontal plane of the body into sextants. When the vector $-\hat{i}'$ is translated into the reference system in such a way that its origin coincides with the origin O , its projections $-\hat{i}'_1$, $-\hat{i}'_2$, and $-\hat{i}'_3$ upon the reference axes faithfully describe (in a proportional way) the RS-T junction displacements in the extremity leads. The subscript simply denotes the lead in question.

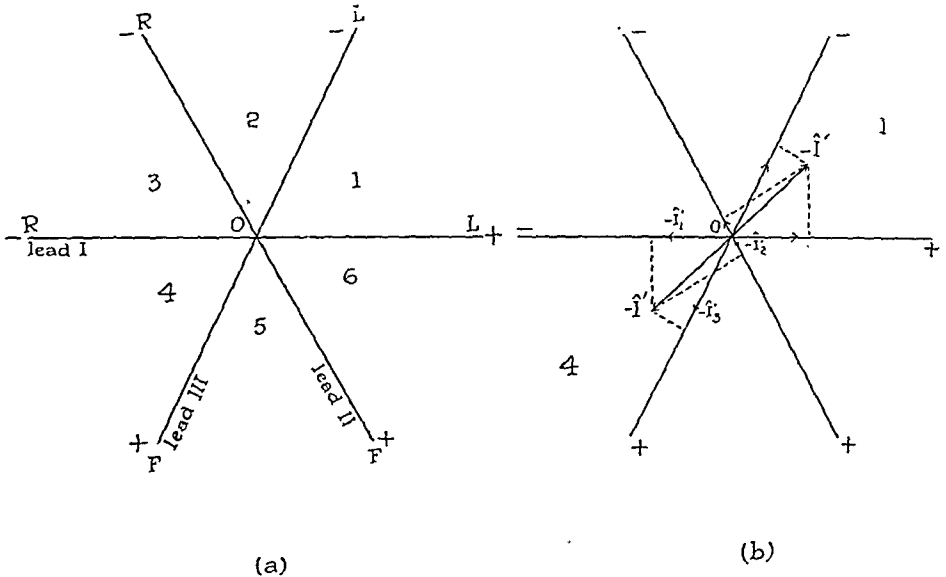


Fig. 1.—*a*, The triaxial reference system formed by translating the sides of the Einthoven triangle. The frontal plane of the body is thus divided into sextants. Sextants 5 and 6 are partially bounded by the positive half, and Sextants 2 and 3 by the negative half, of the three axes. Both sextants 1 and 4 are partially bounded by a positive and a negative half of the same two axes (Leads I and III). *b*, Showing the axis of injury $-\hat{i}'$, drawn outward from the origin O into the first sextant in order to represent the frontal plane projection of the spatial axis of injury $-\hat{i}$, which points from the center of the involved ventricle toward the center or centroid of an injured zone produced by localized pericarditis on the anterolateral ventricular wall. Also shown is another axis of injury $-\hat{i}'$, splitting the fourth sextant. By argument, the latter axis of injury is the one which should be produced by a subendocardial infarct in the same general location as the local pericarditis. The negative sign merely indicates that the quantity $-\hat{i}'$ is of the inverse direction during systole of the electromotive force of injury $2/3 \hat{i}'$ which exists during diastole. When the vector $-\hat{i}'$ for either of the illustrated instances is projected, as indicated, upon the three reference axes, the resulting projections $-\hat{i}'_1$, $-\hat{i}'_2$, and $-\hat{i}'_3$ describe in both magnitude and sense the RS-T junction displacements of the leads denoted by the subscript. The projections are positive or negative (upward or downward) according to their location on a positive or negative half of the reference axes. See text.

For example, subepicardial damage caused by heat, chemical agents, suction, or infection, localized upon the anterolateral aspect of the left ventricle, produces an axis of injury $-\hat{i}'$ (Fig. 1, *b*) which splits the first sextant. Consequently, the RS-T junction displacements are of the discordant type, i.e., positive in Lead I, negative in Lead III, and variable in Lead II. On the other hand, subendocardial damage in the same general location is a structural inverse of the specified subepicardial damage, and should, by the same reasoning, produce an axis of injury $-\hat{i}'$ which splits the fourth sextant (Fig. 1, *b*). In this event the RS-T junction displacement should again be of the discordant type, i.e., negative in Lead I, positive in Lead III, and variable in Lead II. In spite of the fact that an infarct in the same general location in the left ventricular wall is ordinarily essentially subendocardial, these last men-

tioned effects are observed to be the inverse of those which are known to occur clinically and experimentally in association with anterolateral infarction. A similar disagreement exists also between the theory and actual facts pertaining to an essentially subendocardial infarct in other portions of the ventricular wall. The disagreement is likewise of an inverse kind for direct, semidirect, precordial, and esophageal leads. That most infarcts in man are essentially subendocardial is borne out by the significance in relation to infarction which has become attached to certain initial accession deflections (Q) of the extremity leads. Moreover, the transmural infarct almost always has an endocardial surface boundary which exceeds its epicardial surface boundary, with the result, according to the present argument, that its axis of injury should have a direction similar to that which would occur if the latter boundary were absent, as in the case of subendocardial infarct. Here again, the theoretical results prove to be the inverse of those which are actually known to occur with transmural infarction of various portions of the wall of the left ventricle. Inasmuch as the laws which govern the flow of electric currents in volume conductors have been adequately shown³ to apply to problems of the kind under consideration, it follows that the situation which is known to exist after subepicardial injury produced by direct damage cannot be comparable in the details of its pattern to damage resulting from impaired coronary flow. Unlike direct myocardial damage, the damage resulting from impaired coronary flow is attended by a relatively widespread disturbance in the dynamics of local blood flow. The detailed pattern of this disturbance must, it seems, determine which zone will assume the injured state, and which will assume the ischemic state. The nature of the disturbance should also be reflected in the general character and distribution of the relevant pathologic changes. Dr. E. L. Burns* has kindly contributed the following summary of the anatomic changes:

The pathologic changes which occur in the heart of man and dog after rapid occlusion of a large coronary artery have been well described. Karsner and Dwyer,⁸ working with dogs, studied the myocardial changes at various intervals after coronary artery ligation. They found that the affected areas of muscle first became cyanotic, and have an extremely irregular outline. Subsequently, the final area of infarction was observed to be considerably smaller than the early area of cyanosis. This was interpreted as indicating that, although the coronary arteries were terminal in an anatomic sense, there were probably rich possibilities for a collateral circulation. In early infarcts, congestion, hemorrhage, and edema occurred in the stroma, and cloudy swelling, fatty degeneration, and hyaline and granular necrosis occurred in the muscle fibers. After forty-eight hours, fibroblasts were numerous at the margins of the infarct, and contained occasional mitotic figures. Five days after infarction, the transition zone between

*Department of Pathology, Louisiana State University School of Medicine.

necrotic and living heart muscle was demarcated by a well-defined zone of fibroblasts; and, after eighteen days, the infarcted area was composed of a well-formed scar. At this time the scar was fairly dense, moderately vascular, and contained remnants of hyalinized muscle. For the most part, living muscle ended abruptly at the edge of the scar.

The serial anatomic changes which follow infarction of the human myocardium have been well studied by Mallory, White, and Salecido-Salgar.⁹ The earliest changes, grossly, were pallor and dryness of the myocardium. In some instances, blotchy, red-purple areas of focal hemorrhage were found. These changes persisted and became accentuated during the first forty-eight to seventy-two hours. About four days after infarction, a fine yellow border could be seen at the periphery of the infarct. The yellow border proved to be a zone of leucocytic infiltration. By the six- to eight-day period, the zone of infiltration was broader, and, in some regions, was of a yellowish-green color. Eight to ten days after infarction, a reddish-purple zone, composed of newly formed capillaries filled with erythrocytes, had appeared at the periphery of the dead muscle. Concurrently, the volume of the infarct had contracted so that a definite, groove-like depression could be seen at its periphery. The depression had resulted from local removal of dead muscle fibers. By the end of three or four weeks, there remained only small islands of necrotic muscle, surrounded by granulation tissue. By the end of two or three months, the granulation tissue had become transformed into a white, fibrous scar. Whenever and wherever the epicardium or the endocardium was involved, simultaneous and similar changes occurred. Microscopic studies showed that myocardial necrosis was the earliest change, appearing within five or six hours after infarction. When the artery was completely occluded, uniform necrosis resulted. As a general rule, however, the necrosis failed to involve a thin layer of surviving muscle (0.3 to 0.5 mm. thick) which lay beneath the endocardium and extended within the wall along the thebesian veins of the involved region. Additional early changes included hemorrhage, fatty metamorphosis of the muscle fibers, and infiltration of polymorphonuclear leucocytes.

Microscopic evidence of healing commenced about the fourth day, at which time blood capillaries and fibroblasts had appeared at the periphery of the infarct and had begun to grow inward toward its center. Mononuclear cells (probably histiocytes) had begun to remove the necrotic muscle by phagocytosis. The latter process appeared to be progressing rapidly at the periphery of the infarct. By the tenth day, the necrotic muscle fibers had usually been removed completely from a zone 1 mm. wide at the margin of the infarct. Subsequently, removal of necrotic muscle took place more slowly, continuing to completion in about six weeks' time. At about the twelfth day, newly formed collagen fibrils were noted; by the end of the third week, collagen was moderately

prominent; and, by the end of the second or third month, the maximum amount of collagen had been deposited.

Mural thrombi were noted as early as the fifth day, and their organization was complete on about the sixteenth day. Recent or partially organized thrombi were sometimes found in association with relatively old infarcts, which suggested that thrombosis might have been caused by local dilatation of the heart wall, with resulting stagnation of blood in the neighboring portion of the ventricular cavity, rather than by any clotting effect exerted by the infarct itself. Moreover, a subendocardial layer of living muscle was frequently preserved beneath the mural thrombus.



Fig. 2.—A section from the inner layers of the wall of the left ventricle. The patient had suffered from a growing infarct of three months' duration which measured 7 cm. in diameter. It involved the anterolateral wall of the left ventricle. The region shown is from the more recent basal zone of the infarct. The dark smooth margin is the endocardial surface. The subjacent region shows a distinct layer of living muscle. Note the gradient in its abnormal appearance which is everywhere more striking in a direction away from the endocardial surface up to the abrupt line where it terminates at the dark necrotic muscle. In the lower right-hand corner, the necrotic muscle has been partially removed. An electrocardiogram recorded on the day of the patient's death is shown in Fig. 3.

A comparison of the development and healing of myocardial infarcts in man and dogs shows many similarities and few differences. In dogs, hemorrhage is a more prominent feature, and the rate of healing is more rapid. Fibroblastic proliferation begins in about forty-eight hours in dogs, but requires about four days in man. In dogs, the dead muscle usually has been removed from a well-defined peripheral zone by the fifth day, whereas a similar process requires ten days in man. Scar tissue is well developed in dogs by the eighteenth day, but similar changes require two or three months in man.

The faster rate of healing in dogs has been attributed to the smaller size of the infarct and to a more normal residual coronary arterial tree.

In man, the residual coronary arterial tree is usually narrowed by atherosclerosis. A near certainty in man and a proved fact in dogs are the considerable extent to which the early zone of ischemia exceeds the final zone of infarction. The available pathologic evidence, therefore, suggests a general pattern similar to that shown in Fig. 4. On the other hand, Fig. 2 illustrates the surviving layer of subendocardial muscle which is observed in myocardial infarction in both man and dog. This section was obtained at necropsy from the heart of the same subject from whom the electrocardiogram (Fig. 3) was recorded.

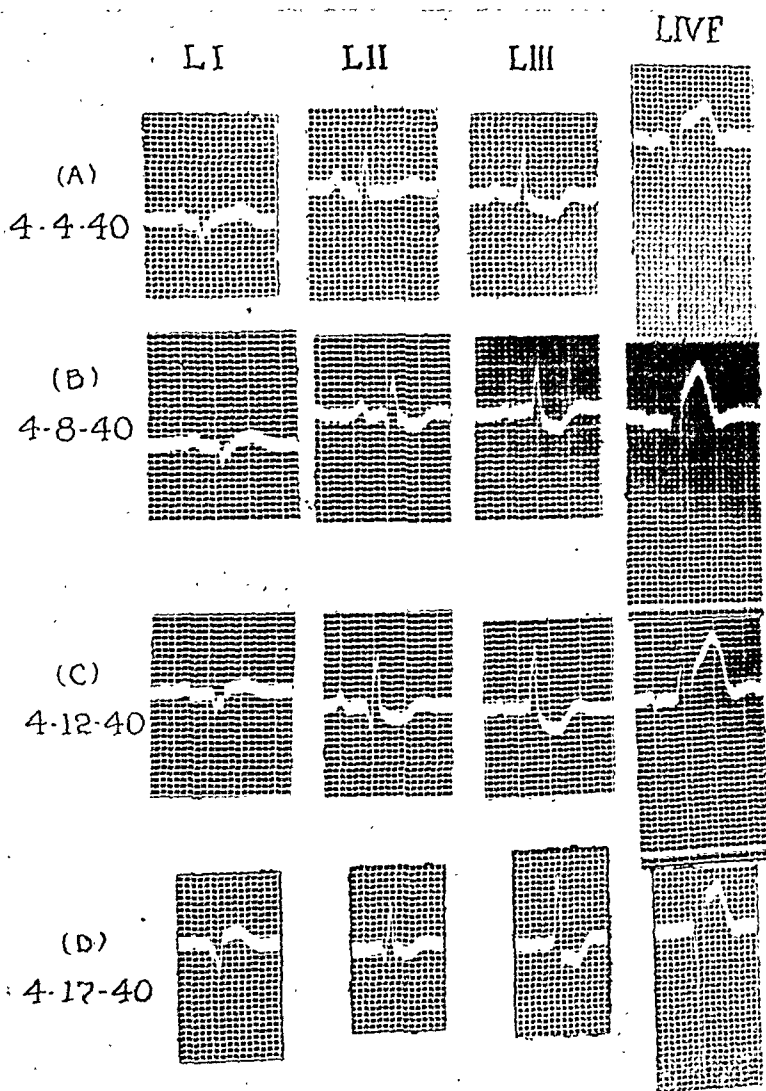


Fig. 3.—Curves A, B, C, and D are serial electrocardiograms recorded from a white male laborer, aged 42 years, who had been suffering from cardiac pain for three months. He had had high blood pressure for several years. The curves were considered diagnostic of fairly recent infarction of large dimensions involving the anterolateral wall of the left ventricle. Note the absence of R_1 and the growth of Q_1 . Curve D, recorded on the day of death, shows a distinct injury current shift of the RS-T₄ junction. See legend of Fig. 2.

It has been suggested that this layer of subendocardial tissue survives because it receives nourishment from intraventricular blood by way of the thebesian veins. The layer or a part thereof often persists, however, even beneath a mural thrombus which makes nourishment by this route

impossible. In such instances it is probable that the layer continues to survive because it receives nourishment from a richly anastomosing plexus of arteries, described by Gross,¹⁰ beneath the endocardial surface. In the absence of a thrombus the layer probably receives nourishment from both the thebesian veins and the subendocardial plexus of arteries, and in such cases the possibility of direct imbibition of oxygen from the neighboring ventricular cavity must also be considered.

THE ELECTRICAL REQUIREMENTS

In addition to the implications of certain of the above described pathologic changes are the requirements which may readily be deduced by a critical analysis of the electrical phenomena known to be associated with infarction. These requirements are: (1) The injured zone is, for the most part, a consistent feature of early infarcts. (2) The injured zone is located in the general region indicated by the spatial axis of injury $-i$, which, by rule, points from the center of the involved ventricle toward the center or centroid of the injured region. (3) A corollary of Item 2 is that, if imaginary equipotential surfaces are constructed within the injured zone in such a way as to describe regions during systole throughout any one of which the intensity of incomplete polarization is everywhere the same, the surfaces must be more numerous between the dead zone and the endocardium than between the dead zone and the epicardium of an essentially subendocardial infarct (obviously, in a transmural infarct no such surfaces can separate the dead zone from the epicardium, for the two structures are contiguous). (4) The environment of the injured zone must be such as to enable the zone to continue electrical activity for several weeks in man (and for a more brief period in dogs). (5) The gradual disappearance of the activity of the injured zone must be intimately associated in some manner with, or be dependent upon, the appearance of the sequential and pronounced T-wave changes which are ascribed to perifocal ischemia. Finally (6), the injured zone must be so organized that it undergoes a subnormal change in the intensity of polarization. If the subnormal change occurs during regression of the injured zone, an injury current flows. If the subnormal change occurs during accession of the injured zone (a blocking effect), the field produced and its effects on the RS-T junction will be the same, or nearly the same, even though no injury current flows. It appears unlikely, however, that blocking occurs as a rule.

PROPOSED THEORY OF THE DISTRIBUTION OF INJURY AND ISCHEMIA

In a subendocardial infarct, the zone of injured cells which appears to meet the anatomic and electrical requirements is depicted in Fig. 4, *a*. The proposed theory of the distribution of the injured zone of a transmural infarct is shown in Fig. 4, *b*. The representations have been made highly diagrammatic for the sake of simplicity. As might be expected in the event that the infarct is essentially subendocardial, the injured zone is perifocal with respect to the dead zone. The ischemic zone, as

shown, is semiperifocal with respect to the dead and injured zones. For a transmural infarct, both the injured and the ischemic zones are depicted as semiperifocal with respect to the dead zone.

In Fig. 4, *a* or *b*, the lines drawn within the injured zone which commence upon the dead zone and cut the equipotential surfaces at right angles represent the imaginary paths along which the gradient of intensity of polarization increases most rapidly. They terminate upon the inner surface of the ischemic zone, where polarization is normal, and they terminate upon the neighboring epicardium. Presumably, after the early stages of infarction, the lines contract in the direction of the dead zone.

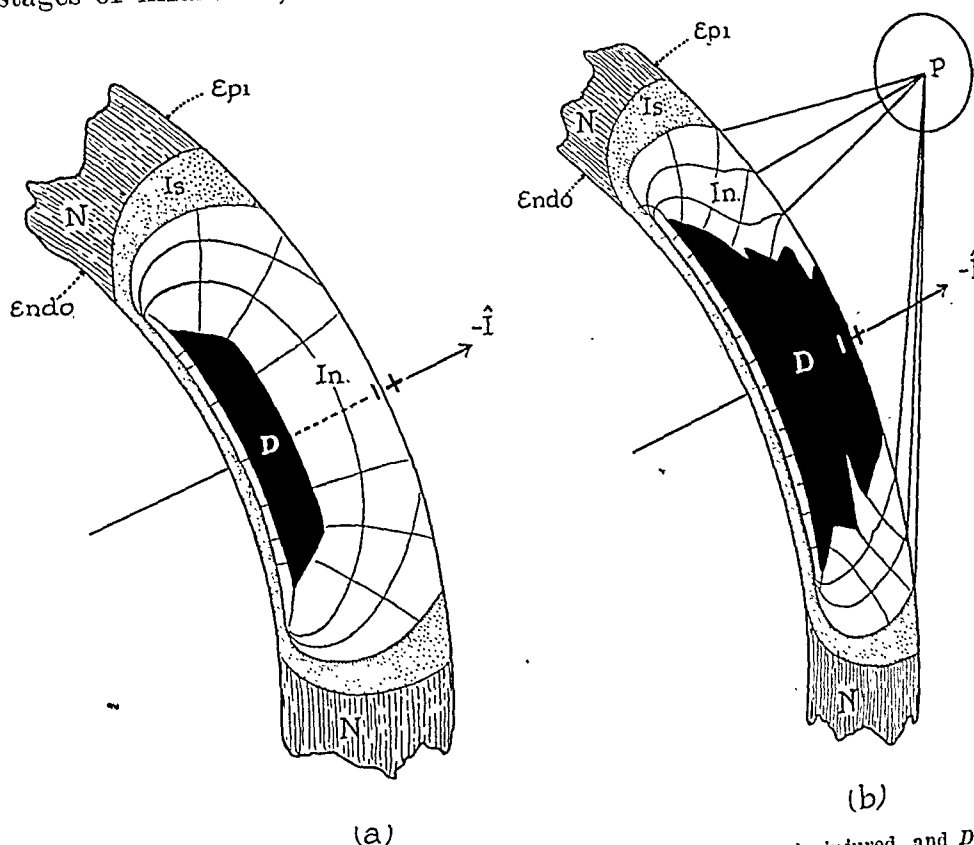


Fig. 4.—For either diagram, *N* is normal, *Is.* is ischemic, *In.* is injured, and *D* is dead, muscle. *a*, Showing the electrical situation as it apparently exists for recent, essentially subendocardial infarcts. *b*, Showing the electrical situation as it apparently exists for recent, essentially transmural infarcts. The equipotential surfaces which envelop or partially envelop the dead zones appear to make contact with one another in the subendocardial layer, whereas they are actually supposed to be separated by relatively small distances. Thus, the gradient of intensity of polarization increases very rapidly in the direction of the ventricular cavity, away from the dead zone. See text. For practical and theoretical purposes it is immaterial whether or not a part of the subendocardial layer persists, as shown, in the electrically ischemic state.

Thus, as the volume of the injured zone diminishes in the direction of the dead zone, the volume of the ischemic zone expands in a similar direction, for muscle units which are recovering from the injured state apparently pass into the ischemic state. When the length of the lines reaches zero, the injured state vanishes and the RS-T junction displacements disappear. Concurrently, as the initially small ischemic zone expands inwardly in a manner which increases its total volume, of necessity the related primary T-wave changes become progressively more pronounced.

Neither the equipotential surfaces nor the gradient of intensity of polarization is to be confused with the equipotential surfaces and the gradient of intensity of the electrical field produced by the injured zone. The former two terms are used in their broader sense merely to describe the source, not the distribution, of the field produced by the injured zone. The distribution of the source is lamellar. The distribution of the field throughout the heart and body may be likened (so far as the extremity leads are concerned) to that which would occur if an electric doublet were situated at the epicardial surface, with its axis collinear with the spatial axis of injury (Fig. 4). The injury potential at a field point p in the vicinity of the epicardial surface (Fig. 4, b) may be regarded as proportional to the sum of the solid angles subtended at p by the many epicardial surface boundaries of the open equipotential surfaces. On further analysis it becomes apparent that all regions enveloped by the closed equipotential surfaces make no contribution to the outside electrical field of injury. Moreover, when the injured zone is of such size and position as to be completely enveloped by the ischemic zone, all equipotential surfaces are closed, and no RS-T junction displacements occur. Clearly, the RS-T junction displacements of the kind under consideration are caused by greater injury at the epicardial surface than at the endocardial surface; that is, by a greater subnormal change in polarization on regression (or on accession, in the case of blocking) at the former than at the latter surface. The subnormal changes in polarization between the two surfaces are immaterial.

Frequently, the early QRS changes which are regarded as characteristic of infarction partially disappear. The disappearance is ascribed to diminution in the size of the injured zone, or, more properly, to the resulting increase in the strength of electrical forces which were previously weak during accession of the injured zone. The subsequent and often greatly delayed disappearance of the primary T-wave changes is ascribed to diminution in the size of the ischemic zone, a change which apparently depends upon further improvement in the local circulation. The subendocardial lamina of the damaged region (Fig. 4) is intimately associated with the Purkinje fibers within it. Consequently, accession of the lamina is insured, and this is an event which might be expected to produce a minute positive deflection at the onset of QRS in unipolar leads obtained by placing the exploring electrode superjacent to the infarct. Actually, minute positive deflections of the kind herein anticipated have been observed,¹¹ and their significance has hitherto been considered uncertain. A potential of this small order of magnitude is not ordinarily manifest in precordial leads. In man and dog, the frequent failure of infarction to produce appreciable prolongation of the QRS complex is regarded as indirect proof of accession of the specified subendocardial lamina.

The author sees no justification, as have some writers,¹² for ascribing any of the RS-T junction effects to a migration toward the ventricular

cavity of potassium which is supposedly released into the interstitial spaces of the infarcted region. If such a release actually occurs, the migration should be outward rather than inward; that is, in the direction of the decreasing gradient of intramural pressure. A phenomenon of this kind may help shape the injured zone into the configuration depicted in Fig. 4. On the other hand, the absorption of potassium could then determine, in part, the rate of diminution of the injured zone.

A NOTE ON THE RS-T JUNCTION DISPLACEMENTS AND SEQUENTIAL
T-WAVE CHANGES IN ANGINA PECTORIS

The above described interpretation of the RS-T junction displacements and sequential T-wave changes caused by infarction has the additional advantage of being readily applicable to changes of a similar kind in curves recorded from certain patients during and immediately after attacks of angina pectoris. The involved region of the ventricular wall may be regarded as consisting initially of a relatively large injured, and a relatively small ischemic, zone. The injured zone may then be further described by means of equipotential surfaces to indicate regions throughout any one of which the intensity of polarization is everywhere the same during systole, and by lines indicating the direction along which the gradient of intensity of polarization increases most rapidly. These lines must commence at the point or points where the temporary deprivation of blood supply is greatest, and must end upon the inner surface of the semiperifocal ischemic zone, and upon the neighboring epicardium, and they must cut all encountered equipotential surfaces at right angles.

If one excludes the QRS changes which result from an alteration of position of the ventricular walls, or from an alteration in the manner of ventricular stimulation, those which appear during the anginal attack may be ascribed to the absence during accession of electrical forces which were previously present within the injured zone. As the injured zone diminishes and vanishes and the RS-T junction displacements concurrently disappear, the QRS changes likewise vanish. In a manner altogether similar to that described for infarction, the diminution of the injured zone contributes to the inward expansion of the ischemic zone. As each unit of muscle recovers from the injured state, it presumably passes into the ischemic state, for, within the injured muscle, the subnormal change of polarization which initially occurs during regression (or during accession if the case is one of local blocking) later becomes normal; whereas, there remains within the injured region a tardy onset of repolarization (ischemic state). An excellent example of the serial electrocardiographic abnormalities which are ascribed to these changes is depicted in a figure recently published by Wilson and Johnston.¹³

There is little doubt that the appearance in sequence of the RS-T junction displacements and the primary T-wave changes reflects a

fundamental law of dynamics of the disturbed myocardial blood supply. Until the pressure within the smaller subdivisions of the coronary circulation falls below that in the ventricular cavity as a result of local coronary obstruction, irrigation across the subendocardial lamina cannot take place. Irrigation of this kind from the ventricular cavity is necessarily confined strictly to the damaged region because the pressure gradients elsewhere are essentially normal. Moreover, irrigation from the ventricular cavity is probably limited primarily to the sphygmie period of systole, at least with lesser grades of local coronary obstruction. So far as the extremity leads are concerned, the electrical effects are adequately described by the development and the decay of the spatial axis of injury $-i$, and by the sequential diversion and reversion of the gradient \hat{A}_{QRST} .⁶

A NOTE ON THE EFFECTS ON THE RS-T JUNCTION AND T WAVE OF
PERICARDITIS ASSOCIATED WITH RECENT INFARCTION

There have recently appeared several admirable attempts^{14, 15} to relate certain of the RS-T junction changes which occur with recent infarction to an associated pericarditis. Because of the complex nature of the problem, empirical as well as experimental studies are likely to lead to confusing results which are difficult to interpret and are of doubtful significance. However, clinical, experimental, and theoretical observations appear to be in agreement with the following comments. When there is a large, recent, transmural infarct of a region of the wall of the left ventricle which does not involve the apex, and when the associated RS-T junction displacements are concordant and positive in the extremity leads, the displacements must be ascribed chiefly to diffuse pericarditis involving the subepicardial muscle layer. If the specified variety of infarct has an apical location, RS-T junction displacements of the kind indicated must be ascribed to the semiperifocal zone of injury of the infarct, and not to a diffuse or local pericarditis. The epicardium over a transmural infarct is supported only by dead muscle which extends inward to the living subendocardial muscle layer, and, under the circumstances, the subepicardial reaction is electrically nil. In general, there is no sound clinical, experimental, or theoretical reason why any electrocardiographic changes should be ascribed to the strictly local pericarditis of a transmural infarct. If there is local pericarditis in the absence of an infarct, or, if a subendocardial infarct is present alone in the same general location, the RS-T junction displacements are similar. If a subendocardial infarct is associated with a superjacent pericarditis, the RS-T junction effects are cumulative. For any one of the three lesions, namely, a recent subendocardial infarct, a recent transmural infarct, and recent local pericarditis, the factor which determines whether the RS-T junction displacements will be concordant, discordant, or of some intermediate form is simply the location of the lesion.

The RS-T junction displacements caused by early diffuse pericarditis tend to obscure temporarily those produced by a recent "anterior infarct"; this statement should hold true in particular for the esophageal leads. The RS-T junction displacements caused by early diffuse pericarditis tend to obscure temporarily those produced by a recent "posterior infarct," especially in the precordial leads. A recent local pericarditis and a recent infarct which are located diametrically across the ventricles from one another tend to produce RS-T junction displacements which are inverse in the extremity leads and may thus nullify each other.

In uncomplicated diffuse pericarditis, the primary T-wave changes consist of concordant inversion. These are reasonably ascribed to the fact that the injured subepicardial zone subsequently acts as if it were ischemic. Intense, apical ischemia may produce the same kind of T-wave change, except that the Q-T interval tends to be prolonged.¹² However, to state that such T-wave changes are caused by extensive infarction¹⁵ is both misleading and theoretically unsound. The association of such T-wave changes with the QRS changes caused by a small apical infarct suggests that the ischemic zone which produces the T-wave changes is semiperifocal with respect to the dead zone of infarct. If, on the other hand, the QRS changes are diagnostic of infarction in a location other than the apex, the specified T-wave changes are best regarded as indicative of the additional presence of apical ischemia or late diffuse pericarditis.

SUMMARY

1. There is a current difference of opinion regarding the interpretation to be placed upon the RS-T junction displacements caused by myocardial infarction.

2. When an electrical situation similar to that which exists with certain varieties of direct subepicardial damage is applied to the ordinary varieties of infarction, according to the laws which determine the flow of electric currents in homogeneous volume conductors, the predicted electrocardiographic effects prove to be the inverse of those which are known to occur clinically and experimentally in association with infarction.

3. Inasmuch as these laws have been shown to apply to problems of the kind herein considered with sufficient accuracy to be useful, it appeared highly probable that the electrical situations caused by direct damage and by infarction, although fundamentally similar, must differ considerably in pattern detail.

4. A summary of the pathologic changes is presented, together with the requirements deduced from a critical analysis of the electrocardiographic changes associated with infarction. The data led to a reasonable definition of the source and sink distribution of the electrical field

of injury and of the neighboring zone of ischemia which are associated with infarction. Moreover, an explanation for the occurrence in sequence of the RS-T junction displacements and the primary T-wave changes is regarded as an integral part of the problem. This sequential relationship, together with heretofore unexplained QRS changes, is thus accounted for incidentally. The RS-T junction displacements in the extremity leads are regarded as the result of the development and subsequent decay of the spatial axis of injury -f. The primary T-wave changes have been ascribed elsewhere to a diversion and subsequent reversion of the spatial gradient of duration of the excited ventricular state. In general, the injured zone caused by recent infarction is perifocal or semiperifocal with respect to the dead zone, depending upon whether the infarct is essentially subendocardial or transmural. The ischemic zone is at first small and semiperifocal with respect to the injured zone. Later, as the injured zone diminishes in the direction of the dead zone and finally disappears, the ischemic zone necessarily undergoes an inward expansion and becomes directly perifocal with respect to the dead zone of a subendocardial infarct, or directly semiperifocal with respect to the dead zone of a transmural infarct. The changes are ascribed chiefly to improvement in the local circulation.

5. The explanation offered for the RS-T junction displacements and the sequential occurrence of T-wave changes as a result of infarction has the additional advantage of being directly applicable to similar but more transient serial changes which are observed in certain patients during and immediately after an attack of angina pectoris.

6. A summary of certain electrocardiographic interpretations is presented which is regarded as tentatively acceptable for curves that reflect the complex combination of infarction and pericarditis.

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ADDENDUM

While this article was in press, a report¹⁶ of two cases of recent subendocardial infarction appeared. Because the extremity leads showed no RS-T junction displacements ascribable to injury, the infarcts were diagnosed as (and found to be) subendocardial. According to the material herein presented, this electrocardiographic feature is regarded as an indication that the infarct may be *strictly* anterior or posterior. The spatial axis of injury $-i$, therefore, lies normal to the frontal plane of the body, and its projection upon the reference axes is zero. The remaining possibility is that the difference in the subnormal change of polarization at the epicardial and the endocardial surfaces is zero. Because the dead zone of infarction fails to involve the subepicardial muscle is not regarded as sufficient evidence for the diagnosis of subendocardial infarction. I have personally observed early anterolateral, as well as diaphragmatic, ventricular wall infarcts which produced the usual striking RS-T junction displacements and were subendocardial.

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THE INFLUENCE OF THE INDIFFERENT ELECTRODE UPON THE PRECORDIAL ELECTROCARDIOGRAM

I. THE NORMAL ELECTROCARDIOGRAM

HANS H. HECHT, M.D., ELOISE, MICH.

THE Committee of the American Heart Association on the Standardization of precordial leads¹ has left unanswered the question whether the position of the indifferent electrode has any bearing on the form of the precordial electrocardiogram, and did not decide which position is most desirable when recording chest leads. Various points on the body surface distant from the heart have been suggested previously as sites for the indifferent electrode (back, left arm, right arm, left foot, and others), and a number of studies bearing on their suitability have been carried out.²⁻¹⁵ The work done thus far has not conclusively established that any one of these electrode positions is superior to the rest, but has shown that large differences in the resulting electrocardiogram may occur if the position of the "indifferent" electrode is changed while the precordial electrode remains in place.

Every electrocardiogram represents the resultant of the potential variations beneath the two recording electrodes, wherever they may be. This is true regardless of whether the electrodes are the apices of an equilateral triangle (standard limb leads) or whether one of them is in immediate contact with the heart (direct leads) or in the precordial region (semidirect leads). The potential differences in the immediate vicinity of the heart are considerably larger than those at a distance from it.¹⁷ Consequently, when one electrode is placed very close to the heart or in contact with it, the position of the second electrode is of little importance as long as it is far from the heart. In leads from the chest wall, however, the potential variations of the exploring electrode are much smaller than in direct leads, whereas the potential variations of the distant electrode remain unchanged. Consequently, the distant electrode has a much greater influence upon the precordial electrocardiogram than upon the curves obtained by direct leads. The influence of the potential variations of the distant electrode upon the precordial electrocardiogram has occasionally been disregarded. The relations between the different kinds of chest leads in common use are illustrated in Fig. 1.

To eliminate the influence of the distant electrode upon the precordial electrocardiogram, Wilson and his associates¹⁸ substituted for

From the Medical Department, William J. Seymour Hospital, Eloise, Michigan.
Aided by a grant of the A. Mendelson Memorial Fund, Detroit, Michigan.
Read before the First Annual Meeting of the American Federation for Clinical Research, Minneapolis, Minnesota, April 20-21, 1912.
Received for publication March 26, 1912.

a single electrode of this kind a "central terminal," connected simultaneously to electrodes on the right arm, left arm, and left leg. Mathematical calculations, based on the theory of the equilateral triangle, and experiments on animals and men have shown that the latter undergoes no large potential variations at any time during the cardiac cycle.^{18, 19} It is held that electrocardiograms taken in this way represent the potential variations of a single electrode, namely, the exploring electrode on the precordium. The connections used are illustrated in Fig. 1, D.

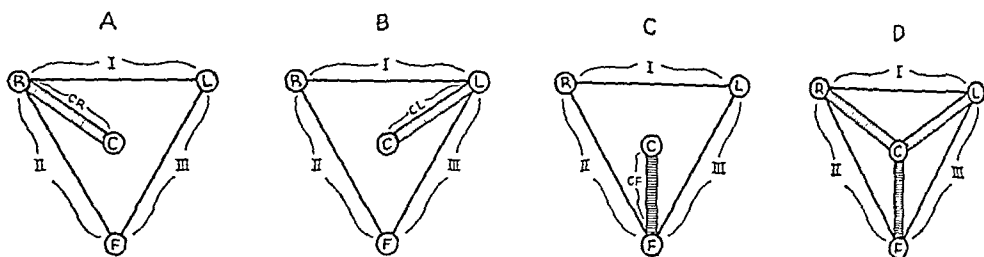


Fig. 1.—L - R represents Lead I, F - R, Lead II, F - L, Lead III.

In A: C - R are chest leads, using right arm as indifferent electrode.

In B: C - L are chest leads paired with left arm.

In C: C - F precordial leads with left leg as distant electrode.

In D: C - (R+L+F) are chest leads using Wilson's central terminal as second electrode. According to Wilson, Barker, and MacLeod $R+L+F = 0$, if the heart is assumed to be the center of an equilateral triangle.

The differences between precordial electrocardiograms taken with different distant electrodes must depend upon the algebraic magnitude of the potential variations at the extremity upon which the "indifferent" or reference electrode is placed. Either calculation or actual recording of these extremity potentials is necessary in order to demonstrate their influence upon precordial leads. Both methods have been used. Recently, Wolferth and Wood²⁰ employed a method by which the influence of the indifferent electrode may be calculated from the standard limb leads. Wilson, Macleod, and Barker²¹ have expressed the extremity potentials in terms of the electrocardiographic deflections of these same leads:

$$V_F \text{ (the potential of the left foot)} = \frac{\text{Lead II} + \text{Lead III}}{3},$$

$$V_L \text{ (the potential of the left arm)} = \frac{\text{Lead I} - \text{Lead III}}{3},$$

$$V_R \text{ (the potential of the right arm)} = -\frac{\text{Lead I} + \text{Lead III}}{3}.$$

Using these formulas, Wilson and his collaborators²¹ and Kossmann and Rader²³ have, by calculation, freed their records of the influence of the distant electrode. With the introduction of the "central terminal" it became possible to record the potentials directly. Unipolar limb leads of this kind have been mentioned occasionally, but their importance in the solution of electrocardiographic problems has not been generally recognized. Their value in estimating the position and

movements of the electrical axis of the heart has been stressed by Kossmann and Johnston,²⁴ and Unghvary,¹³ and lately by Wilson, Johnston, Cotrim, and Rosenbaum.²⁵

The accuracy of these records of extremity potentials depends, of course, on the assumption that the "central terminal" is really a neutral electrode, i.e., does not undergo appreciable changes in potential. It has been pointed out that even though the sum of the potentials of the three extremities, when they are connected to the central terminal, may not always be zero, nevertheless the potential variations of the "central terminal" must be very small compared to those of any of the extremities alone.²⁶ Experiments by Eeky and Fröhlich¹⁹ have shown that this conclusion is valid, and, in the case of normal subjects, the greatest potential variations of the "central terminal" do not exceed 0.3 mv. at any time during the QRS interval. For practical purposes, then, the "central terminal" may be regarded as neutral, and records taken with it represent a close approximation of the potential variations of the single electrode with which it is paired. A right arm—"central terminal" lead, for instance, records the potential variations of the right arm alone. It was thought that, by recording the standard limb leads, the extremity potentials (unipolar limb leads), and a number of precordial leads, the influence of the indifferent electrode upon the precordial electrocardiogram in leads CR, CL, and CF might be studied more satisfactorily than by any other method.

MATERIAL AND METHOD

Twenty normal persons (nurses, interns, attendants, draftees, and a few non-cardiac patients from the hospital) were examined in this way, and the results have been analyzed and tabulated. All of the electrocardiograms which were obtained were normal. The subjects ranged in age from 11 to 62 years (average, 35 years). The tracings were recorded at 25 mm./sec. (standard speed), using a three-beam Sanborn electrocardiograph. Lead I was recorded simultaneously with each of the other leads. All tracings were taken with the subjects recumbent and relaxed. Thirty different leads were taken on each subject, as follows: (1) Three standard limb leads (0.1 mv. = mm). (2) Three extremity potentials (unipolar limb leads); the electrodes on the right arm, left arm, and left foot, respectively, were paired in turn with the "central terminal" in such a manner that an upward deflection of the string represented positivity of the extremity electrode (left arm wire on extremity electrode, selector switch in Lead I position). The deflections thus obtained are, on the average, about one half as large as deflections usually are in standard limb leads. The records were therefore taken with the electrocardiograph at twice the normal sensitivity (0.1 mv. = 2 mm).

(3) Serial chest leads were recorded from the six points recommended by the Committee of the American Heart Association on precordial leads.¹ Unless otherwise stated, the electrocardiograph was used at normal sensitivity. While the precordial electrode and the connecting wire remained in place, the wire connected to the other terminal of the galvanometer was connected in turn to the electrodes on the extremities and to the "central terminal." It would have been desirable to add to these leads one from the precordium to the back because some observers have placed the "indifferent" electrode in the left

scapular region. This was not done because it was thought undesirable to have the patient change his position. Possible effects of changes in position upon the position of the heart and upon the exploring electrode were thus avoided. Spontaneous changes in the electrocardiogram were ruled out by examining Lead I, which was always taken simultaneously with the other leads. Movements of the exploring electrode were avoided by using a special precordial electrode of the suction type.*

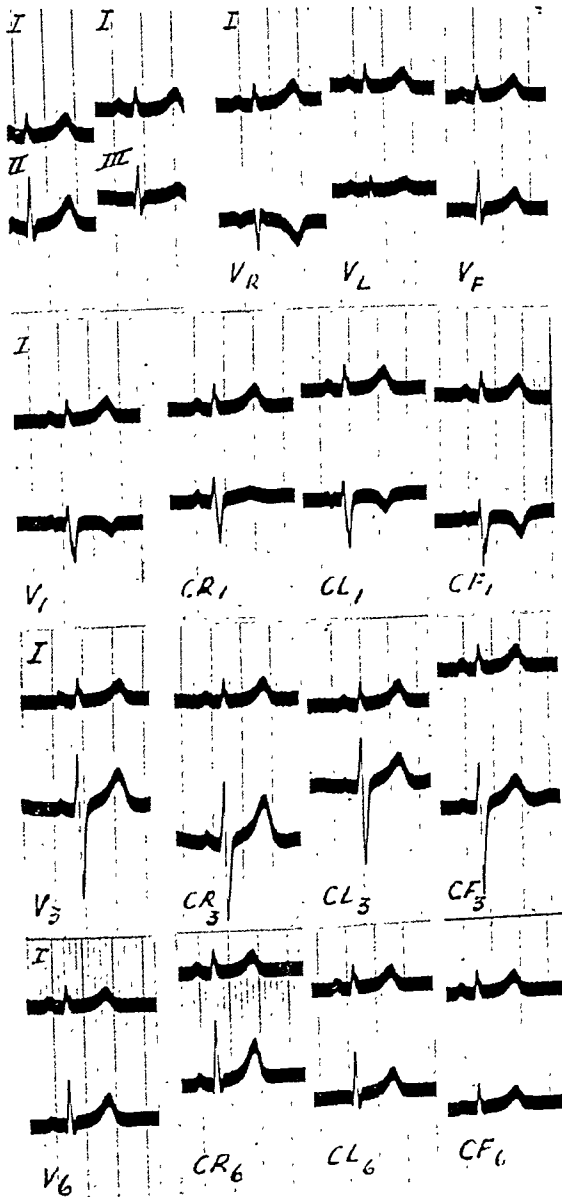


Fig. 2.—To conserve space only 3 of the 6 precordial leads which are recorded are reproduced (V_1 , V_3 , V_6). Miss J. L., 24 years of age, librarian. Normal axis position.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).

2nd row: leads from 4th intercostal space at right sternal border. Note upright T in CR (negative T in V_R) and markedly inverted T in CF (positive T in V_F).

3rd row: leads from 5th rib midway between left sternal border and left mid-clavicular line. Note large P , T , and R waves in CR , and deep S and relatively flat T in CF .

4th row: leads from 6th intercostal space in left midaxillary line. Note high voltage for all deflections in CR , and very small QRS and comparatively flat T in CF .

Lead I simultaneously, chest leads at N/sens.

*Manufactured by the Nichols Chase Company, Detroit, Michigan.

The electrode was $1\frac{1}{2}$ inches in diameter. The suction was strong enough to keep the electrode in position as long as necessary, and its pressure was constant at all times. It was found that better contact was maintained with this type of exploring electrode by using an electrode jelly which did not contain the powdered pumice that is usually present in commercial preparations.

The "central terminal" was arranged as follows: Each extremity electrode was connected to an insulated wire of suitable length. The other end of each wire was soldered to one terminal of a 5000-ohm resistor. The unused terminals of the resistors were then soldered to a wire which was connected to the proper terminal of the electrocardiograph.¹⁸

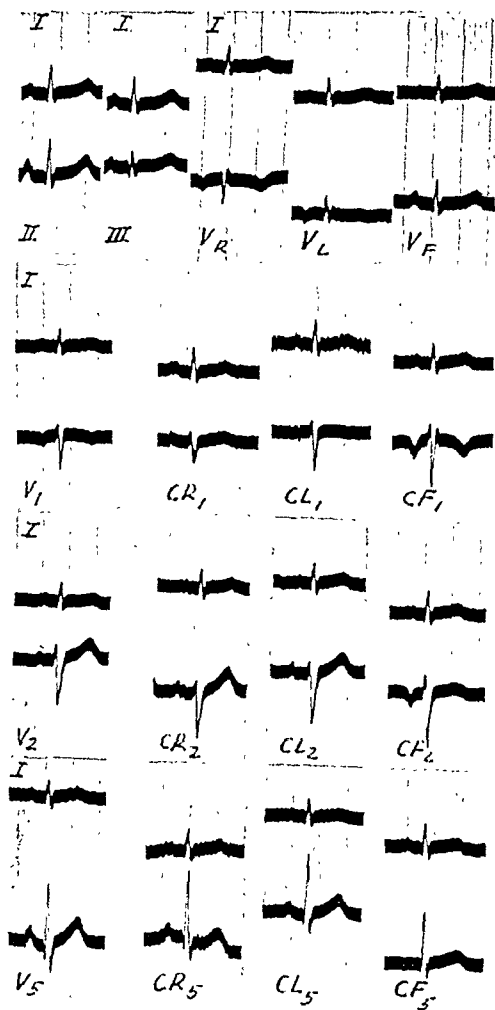


Fig. 3.—To conserve space only 3 of the 6 precordial leads are reproduced (V_1 , V_2 , V_5). Mrs. M. N., 52 years old, schizophrenia (untreated). Normal axis position. Top row: standard leads (N/sens.), extremity potentials (2N/sens.). 2nd row: leads from 4th intercostal space at right sternal border. Note marked inversion of P , QRS , and T in CF (positive P , QRS , and T in VF) and upright P and T in CR , with low voltage of QRS (unfavorable lead). 3rd row: leads from 4th intercostal space at left sternal border. Note that large S waves and inverted P are still present in CF , together with flat but now positive T waves. 4th row: leads from 6th intercostal space in left anterior axillary line. Note isoelectric P in CF , together with small S (S wave present in VF) and flat T . Large deflections in CR . Lead I simultaneously, chest leads at N/sens.

RESULTS

1. QRS complex.—In normal subjects the unipolar right arm lead (V_R) displays, during the QRS interval, a large downward deflection which is preceded or followed by a small positive deflection. The resultant QRS complex somewhat resembles that obtained from the right

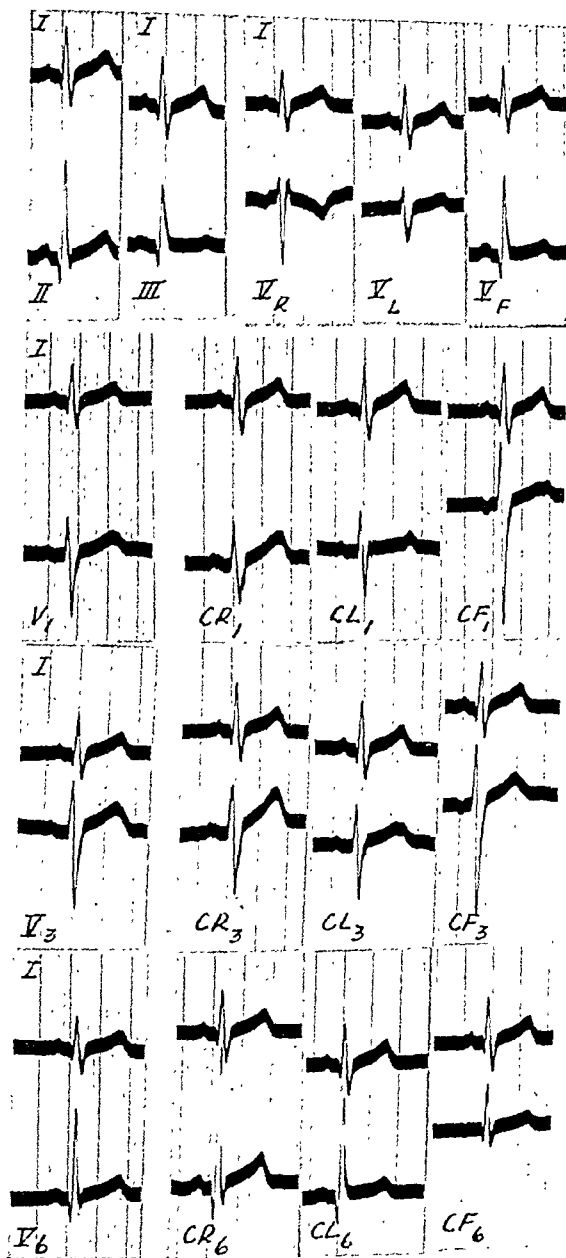


Fig. 4.—To conserve space only 3 of the 6 precordial leads are reproduced (V_1 , V_3 , V_5). Dr. B. Sh., 29 years of age. Tendency to right axis deviation.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).

2nd row: leads from 4th intercostal space at right sternal border. Note inverted P and large S in CF (positive P and large R in V_F). High amplitude in CF for all deflections, low voltage in CR.

3rd row: leads from 5th rib midway between left sternal border and midclavicular line.

4th row: leads from 7th rib in left midaxillary line. Note small total deflections for QRS in CF, with relatively large S waves (high R in V_F). Largest amplitudes in CR. Absent S in CL (large S in V_L).

Broad top of S waves in V_L results in slurring and notching of QRS in CL_1 , CL_2 , and CL_6 .

Lead I simultaneously, chest leads at N/sens.

side of the precordium (Leads V_1 , V_2), or that obtained in experiments on animals by leading from the ventricular cavities; the attachment of the right arm to the trunk is opposite the large valvular openings at the base of the heart, so that the negativity of the ventricular cavities is reflected to the extremity. The uniformity of the QRS pattern of V_R is apparent from the figures given in Table I. The QRS pattern of the left arm (V_L) and left leg (V_F) leads is much more variable. This was noted before by Kossmann and Johnston.²⁴ In our series of 20 cases, R varied in V_L from 0.03 mv. to 0.47 mv., and QS (the largest downward deflection—either Q wave or S wave), from 0.01 mv. to 0.56 mv.; R varied in V_F from 0.15 mv. to 1.12 mv., and QS from 0 to 0.15 mv. If, in extremity potentials, downward deflections represent the negativity of the endocardial surface or the ventricular cavities, upward deflections reflect the positivity of the epicardial ventricular surface.²⁵ The largest upward deflection is found in the lead from that extremity which best reflects the positivity of the epicardial surface of the heart, particularly of the left ventricular wall. In left axis deviation large R waves occur in Lead V_L , indicating that in this case the potentials of the left ventricular surface are transmitted to the left arm. In right axis deviation the left ventricular surface seems to face more toward the legs, and this would favor the appearance of large R waves in V_F . Marked left or right axis deviation is not observed in normal subjects, but normal curves often show features of the one or the other ("right types" and "left types").²⁶ The twenty normal subjects were divided into three different groups, as follows: 8 who showed a tendency to right axis deviation ($\alpha \sim 90^\circ$), 8 who had no axis deviation ($\alpha \sim 60^\circ$), and 4 who had a tendency toward left axis deviation ($\alpha \sim 30^\circ$). As shown in Table I, the subjects in group $\alpha \sim 90^\circ$ displayed large R waves in V_F , and ventricular complexes characterized by large negative deflections in Leads V_R and V_L . This suggests that the negativity of the base of the heart and the ventricular cavities is transmitted to both the right and the left arm when the heart is in a vertical position. The positivity of the epicardial surface of the left ventricle, on the other hand, is transmitted to the left leg (Fig. 5). In the group $\alpha \sim 30^\circ$, large R waves occurred in Lead

TABLE I
THE VENTRICULAR DEFLECTION IN EXTREMITY POTENTIALS*
(IN TENTHS OF MV.)

	V_R				V_L				V_F			
	RS	R	QS	T	RS	R	QS	T	RS	R	QS	T
Group $\alpha \sim 30^\circ$	6.94	0.96	4.06	-2.07	4.54	2.55	0.42	1.39	4.24	1.91	0.79	0.97
Group $\alpha \sim 60^\circ$	4.42	0.42	2.69	-1.28	2.60	1.03	0.37	0.43	4.34	2.42	0.70	1.03
Group $\alpha \sim 90^\circ$	5.92	1.01	3.60	-1.28	4.66	0.69	2.41	0.51	7.76	5.46	0.70	1.14
Total	5.76	0.80	3.45	-1.53	3.93	1.42	1.07	0.78	5.45	3.26	0.75	1.05

*To conserve space, neither range nor standard deviation is given for any of the data presented. This omission seems justified because the figures are presented as an illustration, rather than to state statistical facts. When it was necessary to give further detailed figures, the additional data are mentioned in the text.

V_L , which suggests that in this case the potentials of the left ventricular surface were transmitted to the left arm (Table I). As regards the average size of R in Leads V_L and V_F , the group $\alpha \sim 60^\circ$ occupied an intermediate position. Although the different groups differed significantly with respect to the size of R and S in Leads V_L and V_F , the form of QRS in V_R was similar in all of them.

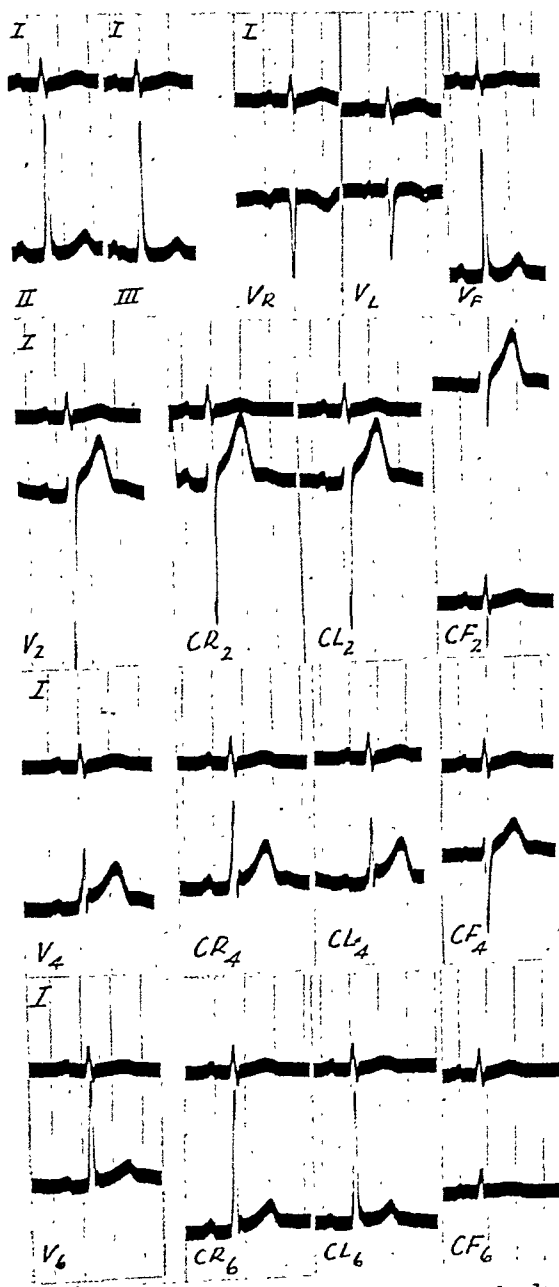


Fig. 5.—To conserve space, only 3 of the 6 precordial leads are reproduced (V_2 , V_4 , V_6). Dr. F. St., 27 years of age. Tendency to right axis deviation.
 Top row: standard leads (N/sens.), extremity potentials (2N/sens.).
 2nd row: leads from 4th intercostal space at left sternal border. Note marked increase in total amplitude of CF with large S waves (large R in V_F), and similarity of CR and CL (similarity of V_R and V_L).
 3rd row: leads from 5th intercostal space in left midclavicular line. Note marked differences in direction of QRS in CF, as compared to other combinations (marked difference in V_F , V_R , V_L). High P, R, and T in CR (inverted P, QRS, T in V_F).
 4th row: leads from 7th rib in left midaxillary line. Note abnormally small deflection in CF (marked distortion by large V_F).
 Lead I simultaneously, chest leads at N/sens.

Table II indicates that CR leads yield higher R waves than the other leads, regardless of whether axis deviation is or is not present. In leads from the left side of the precordium (CR_5 and CR_6), all the deflections which are tabulated (RS, R, and QS) were larger in CR than in the other leads. This was true of each of the three groups. The potential of the right arm was negative throughout all but a small fraction of the QRS interval. The potentials of the right side of the precordium were predominantly negative, whereas the potential of the left side was positive. For this reason, Leads CR_1 and CR_2 yielded smaller deflections, and Leads CR_4 , CR_5 , and CR_6 yielded larger deflections, than the other chest leads. The average value of the total excursion of QRS in CR_1 was 1.290 mv., as compared to 1.449 mv. and 1.781 mv. in Leads CL_1 and CF_1 , respectively. Similar data were obtained in Leads CR_2 , CL_2 , and CF_2 . On the other hand, when the left foot electrode was used as reference point the deflections in leads from the left side of the precordium (CF_4 , CF_5 , and CF_6) were much smaller than in CR or CL leads from the same region. The difference in QRS excursion between CF and CR leads was least pronounced in cases in which there was a tendency toward left axis deviation and most marked when right axis deviation was present. The small R waves in V_F in group $\alpha \sim 30^\circ$ (Table I) had relatively little influence upon the precordial records, but the large R waves in V_F in group $\alpha \sim 90^\circ$ had an important effect. As shown in Table II, the average total QRS excursion in leads from the left midaxillary line were as follows: group $\alpha \sim 30^\circ$, 2.020 mv. in CR_6 , 1.463 mv. in CL_6 , and 1.280 mv. in CF_6 ; group $\alpha \sim 90^\circ$, 2.029 mv. in CR_6 , 1.547 mv. in CL_6 , and only 0.856 mv. in CF_6 . On the average, the total QRS excursion in leads from the left side of the precordium in this last group was less than half as large in CF leads as in CR leads. These relations were reversed in leads from the right side of the precordium and near the base of the heart (CF_1 , CF_2). Since the QRS deflections in V_L leads are usually intermediate in form between those in Lead V_R and in Lead V_F , CL leads are likewise intermediate between CR and CF leads as regards the form of QRS; this was not the case in group $\alpha \sim 30^\circ$, in which slight left axis deviation was present. In this group V_L displayed large R waves which distorted the precordial electrocardiogram in CL leads in the same way as the large R waves of Lead V_F distorted these curves in group $\alpha \sim 90^\circ$ (Table II).

When Wilson's central terminal (CT) was used as the reference point, precordial curves of essentially the same kind were obtained in all these groups ($\alpha \sim 30^\circ$, $\alpha \sim 60^\circ$, $\alpha \sim 90^\circ$) (Table II). This indicates that a shift of the electrical axis has practically no influence on the precordial electrocardiogram when the latter is recorded in this way. This has been pointed out previously.²⁶ The individual deflections never reached their largest or smallest size, and the QRS group never

TABLE II

THE INITIAL VENTRICULAR DEFLECTION IN PRECORDIAL LEADS*
(IN TENTHS OF MILLIVOLT)

		RS				R				QS			
		CR	CL	CF	CT	CR	CL	CF	CT	CR	CL	CF	CT
V ₁	$\alpha \sim 30^\circ$	13.33	14.62	14.68	14.10	4.50	3.50	2.95	4.00	6.95	10.56	9.45	8.32
	$\alpha \sim 60^\circ$	11.57	15.90	17.50	14.56	3.38	2.44	2.40	2.46	6.88	11.40	13.08	10.12
	$\alpha \sim 90^\circ$	13.81	12.85	21.24	14.85	4.25	3.26	3.95	3.48	7.45	7.59	15.88	8.73
	Total	12.90	14.49	17.81	14.47	4.04	3.09	3.11	3.30	7.09	9.85	12.80	9.06
V ₂	$\alpha \sim 30^\circ$	18.83	18.88	19.60	18.10	9.32	4.52	5.02	5.62	8.60	13.93	12.31	10.92
	$\alpha \sim 60^\circ$	16.49	20.10	20.60	18.35	4.86	4.18	3.76	4.14	10.34	14.10	15.36	12.73
	$\alpha \sim 90^\circ$	21.08	19.85	28.65	23.85	5.94	4.86	5.54	5.50	12.86	12.60	19.38	16.08
	Total	18.80	19.61	22.25	20.10	6.71	4.49	4.77	5.09	10.53	13.54	15.68	13.24
V ₃	$\alpha \sim 30^\circ$	19.23	16.44	14.18	18.40	9.02	5.40	5.62	7.22	7.54	9.53	8.38	8.84
	$\alpha \sim 60^\circ$	18.00	17.08	16.35	17.94	8.48	5.55	5.00	6.17	7.61	9.78	9.53	9.64
	$\alpha \sim 90^\circ$	19.40	16.90	26.42	20.40	7.30	5.40	6.94	6.37	10.91	9.10	17.00	12.72
	Total	18.88	16.81	18.98	18.91	8.23	5.45	5.85	6.59	8.69	9.47	11.64	10.40
V ₄	$\alpha \sim 30^\circ$	22.48	18.08	17.85	17.00	15.00	8.98	10.72	12.78	4.28	4.68	4.63	4.28
	$\alpha \sim 60^\circ$	20.95	18.48	16.70	17.85	13.35	10.12	9.46	10.70	5.50	5.98	6.35	5.12
	$\alpha \sim 90^\circ$	25.54	20.45	18.62	20.04	17.08	14.12	6.97	12.61	6.00	3.82	9.28	5.74
	Total	22.10	19.10	17.72	18.30	15.14	11.07	9.05	12.03	5.26	4.83	6.75	5.05
V ₅	$\alpha \sim 30^\circ$	25.08	17.60	18.30	20.35	19.65	12.81	13.70	15.63	2.50	2.03	2.10	2.55
	$\alpha \sim 60^\circ$	21.20	17.55	13.95	17.71	17.08	13.25	10.22	13.72	2.11	2.22	1.54	2.00
	$\alpha \sim 90^\circ$	24.90	20.43	14.20	19.00	21.35	17.96	8.41	15.38	3.13	1.61	2.88	2.88
	Total	23.73	18.53	15.48	19.02	19.36	14.67	10.78	14.91	2.91	1.95	2.17	2.48
V ₆	$\alpha \sim 30^\circ$	20.20	14.63	12.80	16.30	15.53	10.13	9.17	12.30	2.23	2.07	1.33	1.85
	$\alpha \sim 60^\circ$	18.42	13.20	10.58	14.81	15.12	11.28	7.32	11.10	1.25	1.00	1.07	1.01
	$\alpha \sim 90^\circ$	22.24	18.78	8.50	15.82	17.85	15.31	4.12	11.94	2.46	1.35	1.43	1.43
	Total	20.29	15.47	10.63	15.64	12.83	12.23	6.87	11.78	1.98	1.47	1.28	1.43

*See footnote Table I.

showed its largest or smallest excursion in the central terminal leads, but always in leads in which the distant electrode was on one of the extremities. Considering the small number of samples, Table III shows a close agreement between the mean values of the sums of the heights of the deflections in CR, CL, and CF leads, divided by three, and the mean heights of the corresponding deflections in the leads obtained with the central terminal. Since the potential of the central terminal is necessarily at all times the mean potential of the three extremity electrodes, this result is predictable on theoretical grounds.

TABLE III

COMPARISON OF VALUES FOR INITIAL VENTRICULAR DEFLECTION IN PRECORDIAL LEADS
WHEN A "CENTRAL TERMINAL" IS USED, WITH THE SUM OF THE VALUES
FOR ELECTRODES ON LEFT ARM, RIGHT ARM, AND LEFT FOOT
(IN TENTHS OF MV.)

	RS		R		QS	
	CR + CL + CF	CENTRAL	CR + CL + CF	CENTRAL	CR + CL + CF	CENTRAL
	3	TERMINAL	3	TERMINAL	3	TERMINAL
V ₁	15.67	14.47	3.38	3.30	9.91	9.06
V ₂	20.33	20.10	4.99	5.09	13.25	13.24
V ₃	16.22	18.91	6.51	6.59	10.27	10.40
V ₄	19.61	18.30	11.75	12.03	5.61	5.05
V ₅	19.25	19.02	14.60	14.91	2.01	2.48
V ₆	15.46	15.64	10.61	11.78	1.58	1.43

2. P waves.—The mean electrical axis of the normal auricular deflection is less variable than the mean electrical axis of the QRS complex, and no pronounced variations in the form of the P wave were encountered in the present series. This deflection was always upright in the standard limb leads, always inverted in V_R , and always upright in V_F . High, positive P waves occurred in all precordial leads when the indifferent electrode was on the right arm. Flat or inverted P waves were the rule in CF leads. When the central terminal or the left arm was the reference point, intermediate values for the P wave were obtained; in the present series of normal subjects the average height of the P deflection in Lead CR_6 was 0.149 mv., in Lead CL_6 it was 0.072 mv., in Lead CF_6 , minus 0.004 mv., and, in Lead V_6 (central terminal), 0.076 mv. Isoelectric P waves were noted in one case when the central terminal was used as the reference point, in 2 cases when the left arm was so used, and in 8 cases when the left leg was used as the reference point. Inverted P waves were present only in CF leads, and occurred in these leads in 6 subjects. In only 6 instances (30 per cent) were positive P waves encountered in Lead CF_6 .

3. T waves.—Uniformity in the position of the mean electrical axis of T is a striking characteristic of the normal electrocardiogram. Slight shifts to the right, which are often noted in the mean axis of QRS, do not occur in the axis of T in normal subjects. Inversion of the T wave in Lead I is, in other words, distinctly abnormal. Moderate shifts to the left are occasionally encountered (inverted T waves in Lead III). The normal T-wave pattern in the unipolar limb leads (extremity potentials) is similar to the normal pattern of the auricular deflection; the T wave is uniformly downward in V_R and uniformly upright in V_F (Table I). Large positive T waves are seen in CR leads, whereas flat T waves are the rule in CF leads. The height of the T wave in CL leads depends on the magnitude and direction of T in Lead V_L . Since T in this lead is usually upright, the T wave in CL leads tends to resemble that of the CF leads. Whatever connection was used, the T waves were upright in most of the precordial leads which were taken. Inverted T waves were present eight times in Lead CF_1 , and seven times in Lead CL_1 , but inverted T waves were never seen in CR_1 . Diphasic T waves were present three times in Leads CF_1 and CL_1 , and once in Lead V_1 (central terminal). In normal subjects with a tendency toward left axis deviation of the QRS complex, the mean axis of T also tends to shift slightly to the left. The largest T waves in Lead V_L occurred in the group $\alpha \sim 30^\circ$ (Table I), whereas the two other groups ($\alpha \sim 60^\circ$, $\alpha \sim 90^\circ$) showed high T waves only in Lead V_F .

DISCUSSION

Although the influence of the position of the reference electrode upon the precordial electrocardiogram in normal subjects is rarely very striking, it is significant enough to warrant careful consideration.

That the potential variations of the extremity which is used as the reference point are responsible for distortion of the precordial electrocardiogram is to be expected. Their influence can be demonstrated by recording them directly by means of unipolar limb leads (extremity potentials). The distortion is most pronounced when the extremity used as the reference point is the one which displays the largest potential variations. The extremity which is least desirable as a reference point varies from subject to subject with the average direction of the electromotive force produced by the heart. Unipolar leads from the left arm show large deflections when left axis deviation is present ($\alpha \sim 30^\circ$). The potential variations of the left leg are large when the electrical axis is nearly vertical ($\alpha \sim 90^\circ$). The potential variations of the right arm are much more uniform in normal subjects than those of the other extremities. In many respects they resemble those which have been recorded from the ventricular cavities in animal experiments. They are not greatly influenced by axis deviation unless it is extreme. Consequently, if the right arm is used as the reference point in recording precordial leads from normal subjects, the results are much more uniform than when the left arm or the left leg is employed. Since the largest deflections are downward when the exploring electrode is placed on the right arm (Lead V_R), the potential variations of this extremity are of a kind which tends to produce upward deflections when this electrode is shifted to the chest and the indifferent electrode is placed on the right arm. The uniformly negative potential of the right arm during the greater part of the QRS interval must increase the height of the deflection in CR leads, which represent positivity of the precordium. The R waves of these leads are, for this reason, unusually large as compared to the R waves of other chest leads. This is shown in Table II; it has been stressed by many recent investigators.^{2, 5, 6, 14, 16} The fact was known to Einthoven and de Lint²⁷ as early as 1900, i.e., before the introduction of the string galvanometer! However, it has not been sufficiently emphasized that the increased size of R under these circumstances is the result of a summation of the effects of the heart upon the potentials of two electrodes (precordial and right arm). The argument that CR leads are best because they yield the largest deflections is not sound, for it can be clearly demonstrated that the increased height of the deflections is caused by the large negative potentials of the right arm electrode. For similar reasons it cannot be expected that the left leg, which is so commonly used as reference point, gives more accurate results than any other proposed connection. The high R waves in V_F (Table I) will produce deep S waves and subtract from R waves in CF leads for the same reason that deep S deflections in Lead V_R tend to produce high R waves and diminish S waves in CR leads. Here again we are dealing with a summation of effects, with a distortion of the precordial electrocardiogram. Table II indicates that deflections in apical leads are usually smaller in CF than in CR, CL, or central terminal leads. The potential variations

of the apical region and those of the left leg are similar when the electrical axis is in an approximately vertical position, as is commonly the case in normal subjects, relative to the potential variations of the left ventricular surface. The combination of apex—left leg is therefore really an "unfavorable lead" in Waller's sense. The popular IV F lead belongs to this group.

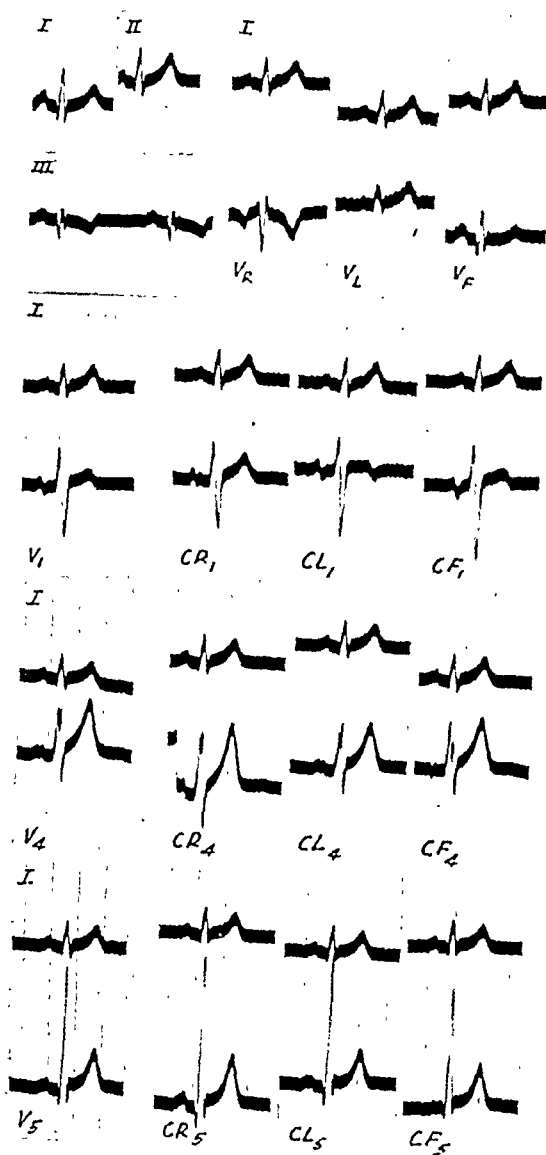


Fig. 6.—To conserve space, only 3 of the 6 precordial leads are reproduced (V_1 , V_4 , V_5). J. C., 35 years old. Draftsman. Tendency to left axis deviation.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).
 2nd row: leads from 4th intercostal space at right sternal border. Note inverted T in CL (positive T in V_L); P waves positive in CR , biphasic in CL , inverted in CF (negative in V_R , isoelectric in V_L , positive in V_F).

3rd row: leads from 5th intercostal space in left midclavicular line. Note split top of R in all leads. Second spike higher than first in CL (large R wave in V_L). First spike higher than second in CF (large Q wave in V_R). These differences remained constant and were not influenced by respiration.

4th row: leads from 6th intercostal space in left anterior axillary line. Relative similarity of pattern except for P waves and slurring of ascending limb of R in CF , caused by large Q waves in V_R .

Lead I simultaneously, chest leads at N/sens.

Our discussion has been confined to general gross effects, but the influence of the reference electrode may make itself felt even in details of the QRS group. A large Q wave in Lead V_F will add to the ascending limb of R in precordial leads and subtract from precordial Q waves if the left leg is used as reference point (Fig. 6); it may even cause a slight notch in the R wave. Large S waves in V_F will diminish the S waves in CF leads, etc. By recording the extremity potential variations the influence of the reference electrode can nearly always be predicted in considerable detail.

The same rules apply, of course, to the configuration of the auricular deflection. A strongly negative P wave was always present in Lead V_R . When the polarity is reversed and the exploring electrode on the arm is replaced by the reference electrode, the effect is to increase the size of the auricular deflection in precordial leads. This explains why CR leads yield such "good results" in the case of the auricular deflections. For similar reasons CF leads result in small, positive, isoelectric, or negative auricular deflections. Since P waves are largest in leads from the right side of the precordium and almost disappear when the exploring electrode is shifted toward the apex,^{24, 26} CF leads have a strong tendency to display inverted P waves in leads from the left side of the precordium. The negative potentials of the leg Lead V_F is not opposed by a significantly positive precordial potential. Whether the P waves are positive, isoelectric, or negative in CL leads depends again on the direction and magnitude of the P deflection in Lead V_L . Such leads resemble CR leads if P is negative in Lead V_L , and CF leads when it is upright in V_L .

The influence of the reference electrode on the T wave of the normal precordial electrocardiogram is rarely very conspicuous because a large positive T wave is an essential feature of the precordial electrocardiogram of normal adult subjects. Slight additions to, or subtractions from, this wave (distortions from the distant electrode) are of little significance. The position of the reference electrode is important in leads from the extreme right side of the precordium, in which the T waves are occasionally flat or inverted. The large positive T waves regularly encountered in Lead V_F cause inversion of the precordial T waves in Lead CF_1 in almost half the cases. They are also responsible for relatively flat T waves in Leads CF_5 and CF_6 . It is conceivable that an unusually large T wave in V_F may cause a diphasic or even an inverted T wave in Leads CF_5 and CF_6 in normal subjects. Such an extreme case was not observed in our group, but it may well explain inversion of T in Lead IV F in a normal person, which was reported by Sodeman.²⁸

The conflicting reports concerning the relative merits of one reference electrode point as compared to others resolve into a question of what type of patients are to be examined. Those with a tendency to left axis deviation will show gross distortion of the precordial electrocardiogram in CL leads; those with right axis deviation will

show more distortion in CF leads. The last is true also of those without axis deviation, as has been pointed out in a previous paragraph, and has been stressed by Deeds and Barnes.²

It is, of course, not feasible to ascertain the direction and amplitude of the potential variations of each of the extremities in every individual patient, and then chose the best connection. With the introduction of the central terminal into electrocardiography this has become unnecessary. The central terminal shows little if any variations of potential, and the results obtained with it are relatively uniform. It is almost as simple to use as any other method, and the materials necessary for its construction can be easily obtained. Whether or not the potential of the central terminal is entirely unaffected by the heart beat is of little practical importance as long as its potential variations are negligibly small or markedly smaller and much more uniform than those of the extremities. That this is the case seems certain from the present study, as well as from theoretical considerations²⁵ and the experiments of Eckey and Fröhlich.¹⁰ The distortion caused by the reference electrode may in exceptional cases be helpful, and in such cases an electrode on one limb alone may be preferable to the central terminal. Chest leads are sometimes employed for better demonstration of the auricular deflections when these are masked or hardly detectable in the standard limb leads. For this purpose the right arm may serve better as the reference point than any other extremity or the central terminal.

When the purpose is to ascertain with greatest accuracy the form of the potential variation of the precordium, the central terminal should be used as the reference point.

SUMMARY

1. Standard limb leads, unipolar limb leads (extremity potentials), unipolar precordial leads, and precordial leads of the CR, CL, and CF types were taken in a series of normal subjects. Analysis of the curves thus obtained justifies the following conclusions:

2. The position of the reference electrode has a considerable effect upon the size and form of the normal precordial electrocardiogram.

3. The potential variations of the left arm in CL leads and the influence of the potential variation of the left leg in CF leads vary with the position of the mean electrical axis of P, QRS, and T. The distortion which occurs in CR leads is not appreciably less than that in CL and CF leads, but is much more uniform in magnitude and in duration when the electrical axes of P, QRS, and T are in a relatively normal position.

4. When a central terminal is employed, the distortion introduced by the reference electrode is eliminated or reduced to a minimum.

The author wishes to thank Dr. F. N. Wilson for his many suggestions in the preparation of this paper.

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QUINIDINE, "PURE QUINIDINE," AND HYDROQUINIDINE

I. TOXICITY

S. A. WEISMAN, M.D.
MINNEAPOLIS, MINN.

COMMERCIAL quinidine is composed of about 80 per cent "pure quinidine" and 20 per cent hydroquinidine. The well-known effect of quinidine in cases of auricular fibrillation is, according to Van Dongen and Sanches,^{1, 2} due to hydroquinidine. These investigators have shown that hydroquinidine lengthens the refractory period and increases the auricular and auriculoventricular conduction time, and that "pure quinidine" does not have these effects, which means that it is more or less inert.

We have been conducting a series of experiments on dogs to ascertain the comparative toxic and pharmacologic effects of quinidine, hydroquinidine, and "pure quinidine." Through the cooperation of Merck and Company, we were furnished with these preparations. However, the purest "pure quinidine" that we could obtain contained about 8 per cent hydroquinidine.

Our first study was concerned with comparing the toxic effects of these drugs on dogs. The drugs were given intravenously in sublethal doses.

TABLE I

GENERAL AVERAGE VALUE OF THE EFFECT OF THE THREE QUINIDINES ON BLOOD PRESSURE, PULSE RATE AND RESPIRATORY RATE

TIME	"PURE QUINIDINE"			COMMERCIAL QUINIDINE			HYDROQUINIDINE		
	B.P.	PULSE	RESPIR.	B.P.	PULSE	RESPIR.	B.P.	PULSE	RESPIR.
Normal	142	154	13	136	164	13	151	152	18
End of Q* injection	38(13)	99	15	52(11)	100	14	94(7)	151	19
5 min. after	34(5)	105	19				127(3)	132	17
15 min. after	40(4)	111	15	60(7)	93	13	114(5)	126	18
30 min. after	66(3)	129	17	68(5)	120	14			
1 hr. after	96(2)	167	20	94(4)	159	15	128(6)	130	22
2 hr. after	112(4)	166	13	112(5)	139	18	147(5)	192	22
3 hr. after	115(4)	138	20	132(7)	115	18	155(2)	204	31
	Death rate, 46.1%			Death rate, 18.2%			Death rate, 0.0%		

The above figures are simply tabulated to give a general view of the effect of the three quinidines on blood pressure, pulse, and respiration.

Because of experimental conditions, the exact time interval could not always be recorded.

The figures in parentheses indicate the number of animals that have been taken into account for the specific time stated.

*Q = Quinidine.

From the Department of Medicine and the Department of Pharmacology, University of Minnesota.

This work was carried out with the aid of a grant from the Graduate School, University of Minnesota.

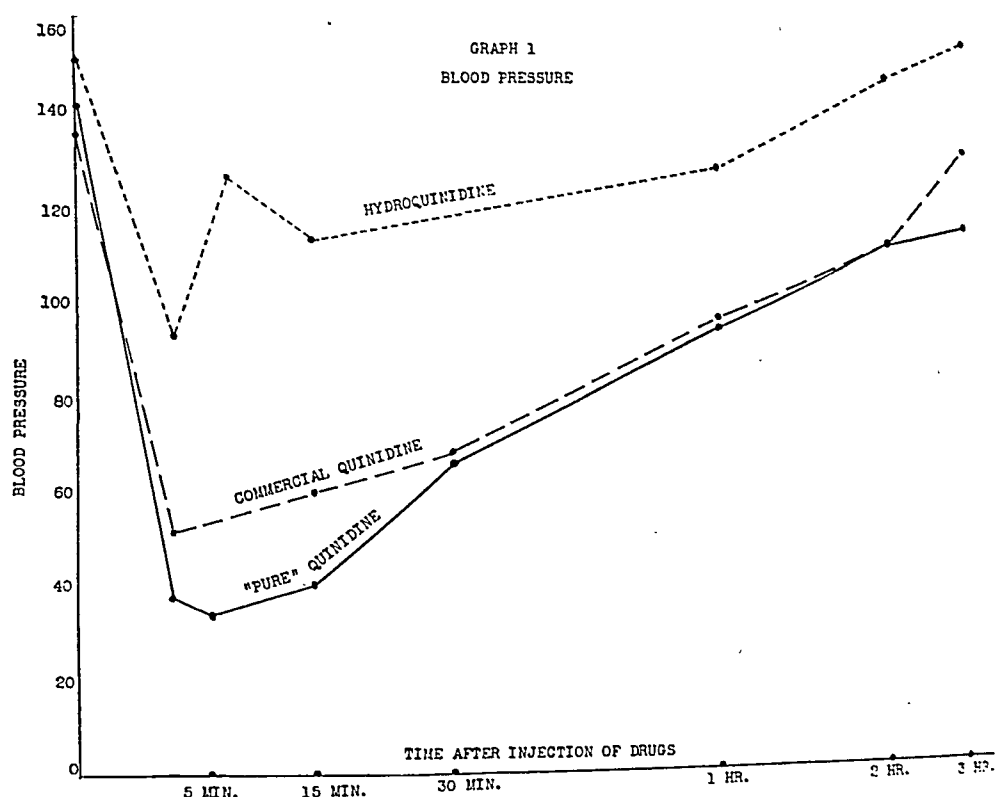
Assistance in the preparation of these materials was furnished by the personnel of Works Progress Administration, official project No. 665-71-3-69.

Received for publication Feb. 25, 1942.

In previous studies we found that 45 mg. per kilo of quinidine was a sublethal dose.³ Comparable doses of hydroquinidine were used; the amount was estimated on the basis of the fact that this drug composes about 20 per cent of the commercial product. A summary of these experiments is shown in Table I.

COMMERCIAL QUINIDINE

Eleven experiments were carried out with this drug. A sublethal dose of 45 mg. per kilo of quinidine was used. There were two deaths, a mortality rate of 18.2 per cent.



HYDROQUINIDINE

Seven experiments were done in this study. In only one dog did we use the actual minimal lethal dose, 9 mg. per kilo, which is 20 per cent of the lethal dose of quinidine. We increased the amounts of hydroquinidine to 20 mg. per kilo. This amount, theoretically, is twice the sublethal dose. There were no deaths in this series of experiments. As the dose of hydroquinidine was increased, convulsions tended to appear about one hour after the administration of the drug. These often lasted for an hour or more, and continued even after the animal recovered from the anesthesia.

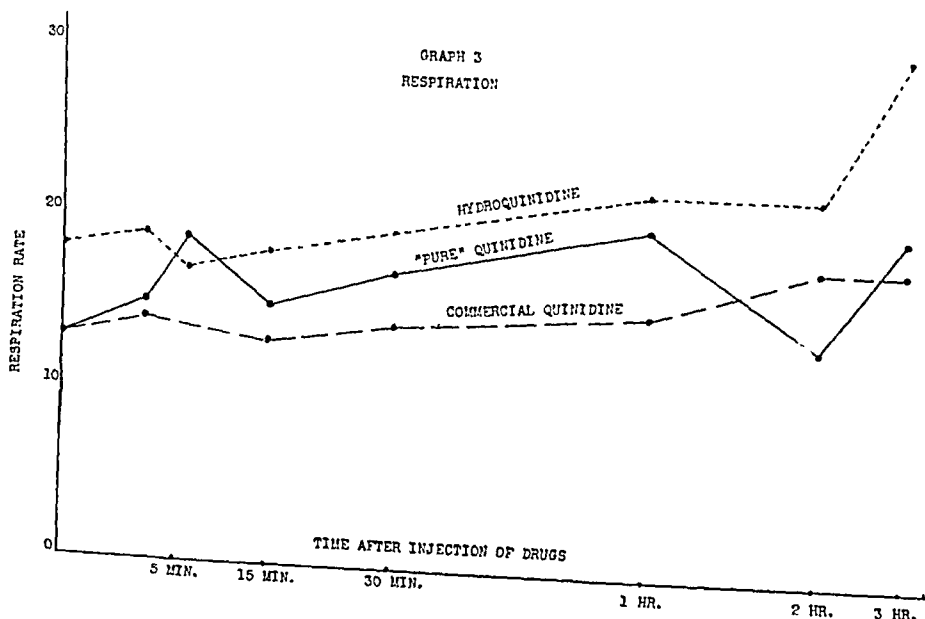
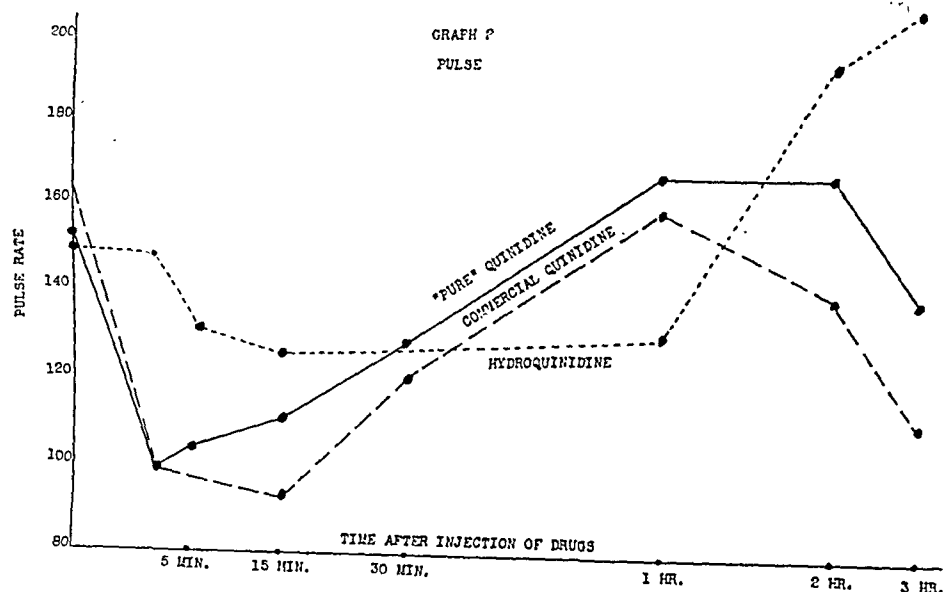
"PURE QUINIDINE"

Sixteen experiments were carried out with this drug. Three studies were made on one dog, using very small doses. Thirteen dogs were given

sublethal doses, 45 mg. per kilo, and six dogs died. In the thirteen experiments in which sublethal doses were used, there was a mortality rate of 46.1 per cent.

BLOOD PRESSURE

The greatest fall in blood pressure followed the administration of "pure quinidine" (Graph 1). The blood pressure did not immediately recover after the initial fall, as it did after giving the other two preparations. The blood pressure after the injection showed a tendency to remain for a longer time at a low level, and often would fall even a little more before tending to rise again. "Pure quinidine" appeared to be the most potent vascular depressant.



The effect of regular quinidine is well known. Usually there is an immediate fall in blood pressure after its administration, after which there is a prompt tendency for the blood pressure to rise again.

Hydroquinidine caused the least fall in blood pressure. The fall after its administration was about one-half that which followed the administration of the other two drugs. The recovery, however, was much more rapid. After a period of about two hours the blood pressure rose above the level at which it stood before the drug had been given.

PULSE RATE

The pulse rate is slowed more by quinidine and "pure quinidine" than by hydroquinidine (Graph 2). The rate remains slower for about 10 minutes longer after giving quinidine than after the administration of "pure quinidine." The initial rate is reached before one hour after giving the drugs. Hydroquinidine is the least depressing on the pulse rate. The effect is very slight. In about one hour the pulse rate begins to increase, and soon reaches a higher level than was present before the administration of the drug.

RESPIRATION

There was no depressing effect on respiration as a result of administering "pure quinidine," regular quinidine, or hydroquinidine (Graph 3). There appeared to be a slight increase in respiratory rate after "pure quinidine" and hydroquinidine.

SUMMARY

1. Quinidine is composed of about 20 per cent hydroquinidine and 80 per cent "pure quinidine."

2. "Pure quinidine" is a marked cardiovascular depressant. It is much more toxic than quinidine in doses equivalent to sublethal doses of quinidine.

3. The mortality rate which resulted from giving quinidine in sublethal doses was 18.2 per cent.

4. The mortality rate as a result of giving "pure quinidine" in sublethal doses was 46.1 per cent.

5. No mortality resulted from using equivalent sublethal and larger doses of hydroquinidine.

6. Hydroquinidine is a very slight cardiovascular depressant.

7. The hydroquinidine fraction of quinidine appears to counteract to a great degree the cardiovascular depressant action of the "pure quinidine" fraction.

Eight patients with chronic auricular fibrillation were treated with hydroquinidine. In not one case was normal rhythm restored. This study will be reported at some future date.

The writer wishes to express his sincere thanks to Dr. A. D. Hirschfelder for much valuable advice and help in carrying out this study, and to George Tamcales for technical assistance.

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Clinical Reports

ANEURYSM OF ONE OF THE SINUSES OF VALSALVA CAUSED BY A CONGENITAL LESION

CASE REPORT

F. J. HIRSCHBOECK, M.D., DULUTH, MINN.

ANEURYSM of one of the sinuses of Valsalva may be part of a more diffuse aneurysm involving the proximal portion of the aortic arch, but may also occur as an isolated entity as a result of syphilis, arteriosclerosis, ulcerative endocarditis, or a congenital lesion. Micks¹ states that twelve, including his case, have been of congenital origin. Usually the right aortic sinus alone is involved. Four instances have been reported in which aneurysms were present in the three sinuses.

There appears to be some confusion in regard to the nomenclature of the aortic sinuses, but for clinical purposes a division into right, left, and posterior sinuses is most acceptable. The right sinus is marked by the fact that the right coronary artery arises from it; the left coronary originates in the left sinus. The posterior sinus may be designated as the "noncoronary" sinus. The sinuses are intracardiac in their anatomic relations. The signs of aneurysm are caused partly by involvement of the aortic ring and partly by secondary pressure on the surrounding cardiac structures. The location of the sinuses determines the direction in which the aneurysm will extend. The right sinus is in juxtaposition to the right auricle and ventricle. The left sinus lies external to the left ventricle and internal to the pericardial sac. Enlargement of an aneurysm of the left sinus may reveal itself on the external topography of the heart because of its relation to the pericardial sac, which is usually at a point to the left of the pulmonary artery; the posterior sinus is located anterior to the right and left auricles.

Since the aneurysms are almost invariably intracardiac, they are often associated with unusual murmurs and thrills. The proximity of the right sinus to the membranous portion of the septum occasionally produces conduction disturbances. Compression by the contiguous heart muscle and lack of freedom of expansion usually prevent the aneurysms from growing very large, but they frequently attain the size of a hen's egg. Since the coronary orifices arise in proximity to the sinuses, they may become aneurysmal by contiguity. Disturbance of the function of the aortic valve is not uncommon. Sinus aneurysms may rupture into the

pericardium, the vena cava, the pulmonary artery, or one of the heart cavities. Death may ensue rapidly with rupture into the pericardium, but when rupture occurs into a heart cavity, the pulmonary artery, or one of the large venous trunks, death does not always occur immediately, and sudden changes in the palpatory and auscultatory signs may be noted: Such signs and symptoms of marked change in the circulatory mechanics develop abruptly and are plainly evident.

In the case reported in this paper, the aneurysm apparently arose at the site of a congenital defect in the aortic ring, and originated in the right sinus. The posterior sinus was rudimentary. Aneurysms which project from the right sinus tend to bulge through the septum between the ventricles, and extend anteriorly into the conus of the right ventricle 1 or 2 cm. below the pulmonary ring. Involvement more to the right will produce bulging into the right ventricle in the region of the tricuspid valve commissure on the anterior or right septal surface, and may cause relative insufficiency or stenosis of the valve. Aneurysms may rupture into the right auricle or ventricle, and, because of encroachment on the interventricular septum, may cause intraventricular conduction defects.

CASE REPORT

A. L. H., a man, aged 20, a student, was admitted to St. Mary's Hospital February 18, 1939, and died February 26, 1939. He was under the care of Dr. F. W. Spicer, and was seen in consultation on February 23, 1939, by Drs. F. W. Spicer and F. J. Hirschboeck.

On admission to the hospital the patient complained of extreme shortness of breath, pain in the chest, vomiting, and disorientation. The history was obtained from the mother, who stated that the patient had had a somewhat similar experience about a month before, when he suddenly began to vomit and had severe pain in his chest, with shortness of breath. These symptoms continued for about three days, and then the patient appeared to improve for about three weeks.

Past History.—The patient had always been very active, and participated in athletics, including football. There was no history of rheumatic fever or any previous suggestion of congenital heart disease, and the patient had always been well except for the diseases of childhood, which were not associated with any complications.

Physical Examination.—The patient was a rather robust white man, 20 years of age; he weighed about 160 pounds.

Examination of the eyes, ears, nose, and throat was negative. The pupils were normal and equal, and reacted to light and in accommodation. It was noted that there was prominent pulsation in the carotid vessels. The veins were not distended in the neck, but were visible in the upper portion of the chest. A pulsation was also observed in the epigastrium. The heart was enlarged diffusely. Careful measurements were lacking. There was a marked systolic thrill over the apex, and a harsh systolic murmur was audible at the lower end of the sternum and in the epigastrium. On admission to the hospital his blood pressure was 300/0. The heart rate was 140. There was no evidence of any abnormality of the lungs. The liver dullness was about two fingerbreadths below the right costal margin. Over the peripheral vessels a pistol-shot sound was audible.

Laboratory Data.—On two occasions the hemoglobin was 91 and 94 per cent, and the erythrocyte count, 4,810,000 and 4,700,000, respectively. The leucocyte count on February 19 was 11,400, and, on February 23, 18,800. A differential

leucocyte count showed 77 polymorphonuclear cells, and 11 small and 12 large lymphocytes. The blood urea nitrogen was 18 mg. per cent, and the creatinin, 2 mg. per cent. Blood cultures on two occasions were negative, and remained negative after the death of the patient. The urine was normal except for a trace of albumin; the specific gravity was 1.024 to 1.030.

A roentgenogram of the chest, taken in bed, showed what seemed to be enlargement of the heart to the right and left, but more particularly to the right. An electrocardiogram showed right axis deviation, low voltage in all the leads, inversion of T_1 , an isoelectric T_2 and T_3 , elevation of ST_1 , and slurring of the QRS in all leads.

The temperature fluctuated from normal to 103° F.

A tentative diagnosis of subacute bacterial endocarditis was made.

On February 23 it was noted that the heartbeat was very rapid (130) and tumultuous. The murmurs were harsh and seemed to be chiefly systolic; they were at the lower end of the sternum and in the epigastrium, as previously observed. The blood pressure at that time was 200/0, and, although the rapidity of the heart made it difficult to interpret the murmurs at the base, it was thought that a diastolic murmur was heard. The next day the heartbeat was less rapid, and a diastolic murmur could be heard plainly at the left border of the sternum and in the aortic area. The diagnosis was aortic insufficiency and tricuspid insufficiency, caused by endocarditis of undetermined origin. On February 26 the patient became rapidly weaker and died.



Fig. 1.—View of the left ventricle and aortic opening. Opening of the aneurysm is plainly seen in the right aortic sinus. Its relative size as compared to the rudimentary posterior sinus is manifest.

Autopsy.—On opening the abdominal cavity the peritoneal cavity was found to contain about 800 c.c. of clear, straw-colored fluid. The liver reached the costal margin in the right midclavicular line. The left pleural cavity contained 600 c.c. of clear, straw-colored fluid, and the right pleural cavity, 300 c.c. There were no pleural adhesions. The pericardium contained 250 c.c. of clear, straw-colored fluid. The heart weighed 445 Gm., the liver, 2,000 Gm., the spleen, 220 Gm., and the kidneys, 350 Gm.

The heart was about one and one-half times the size of the deceased's fist, and the cavities were dilated, mainly on the right side. The cavities of the heart con-

tained fluid blood. There were numerous small hemorrhages under the epicardium, mainly on the right side and along the sinus venosus. The pulmonary valve was normal in appearance. The cusps of the aortic valve were quite unequal; the left and the right cusps were larger than usual, and the posterior cusp was undeveloped and rudimentary. The openings of the left and right coronary arteries were in the normal position. The right aortic sinus was deeper than usual, and, in the deepest portion of the sinus, below the opening of the right coronary artery, the wall of the aorta was the seat of a round defect, measuring about 1 cm. in diameter, through which blood had passed into the right side of the heart. The point of emergence of the aneurysmal cavity, as seen from the inside of the right heart, was sac-like; it measured about 1.2 cm. in diameter, and lay prominently between two of the tricuspid leaflets. The sac-like structure was formed by a thin layer of connective tissue, and at its apex there was an irregular tear about 1 cm. in length; rupture had apparently occurred recently. There were no fresh or old endocardial deposits on the valves or walls of the heart. The mitral valve admitted three fingers and appeared normal.



Fig. 2.—Exposed right side of the heart. The opening of the aneurysm at the tricuspid orifice is shown. Its position and the transmission of the jet toward the cavity of the right ventricle are also noted.

The tricuspid valve admitted four fingers; two of the leaflets were held apart by the encroachment of the aneurysm. The foramen ovale was closed. The interventricular septum was normal. The coronary arteries were normal in appearance. The myocardium was normal in appearance. The wall of the ventricles was moderately hypertrophied, mainly on the right side.

Examination of the lungs showed some punctate hemorrhages on the visceral pleura. The left lung was the seat of marked and diffuse congestion, particularly in the posterior portion of the lower lobe. The right lung was similarly but less

affected. The pulmonary artery appeared to be normal. The spleen had a slightly increased consistency, but was otherwise normal. The kidneys were normal. The liver showed moderate central passive congestion; the periphery of the lobules was somewhat yellowish.

The post-mortem diagnosis was malformation of the aortic valve, with aneurysm of the right aortic sinus which extended through the ventricular wall and emerged as a sac-like projection into the right auricle and encroached upon the tricuspid orifice; rupture of the aneurysm, with formation of a shunt between the aorta and right ventricle: congestion, Grade III, and edema, Grade II, of the lungs; central passive congestion of the liver; bilateral hydrothorax; ascites.

Microscopic examination of the heart showed slight fragmentation, but nothing else abnormal.

This case was interesting because a congenital anomaly of the aortic ring was found, with a rudimentary posterior cusp. There was an aneurysm which arose at the base of the right aortic sinus and extended through the wall of the ventricle into the right auricle; it emerged at the tricuspid orifice, and ruptured in the direction of the right ventricle. Of interest clinically was the extremely high pulse pressure; on one occasion the blood pressure measured 300/0. This is explained in part by the relative aortic insufficiency caused by the proximity of the aneurysm to the aortic ring, and in part by the development of an arteriovenous shunt from the aortic ring into the right side of the heart. These two factors evidently combined to cause the unusual blood pressure. Clinically, it was possible to detect the functional disturbance in the valve, but the anatomic cause was not recognized.

It would seem that the aneurysm was caused by a congenital anomaly and weakness of the aortic valve ring.

NOTE.—The right axis deviation in the electrocardiogram, in view of the extreme hypertension, was thought unusual. William B. Porter, in the *AMERICAN HEART JOURNAL*, Vol. 23, page 468, describes similar occurrences, with rupture of the aortic aneurysm into the pulmonary artery. The analogy between the instances described by Porter and this case, in which aortic aneurysm ruptured into the right side of the heart, is evident.

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QUINIDINE AND POTASSIUM IN THE TREATMENT OF REFRACTORY PAROXYSMAL VENTRICULAR TACHYCARDIA

STEPHEN J. STEMPIEN, M.D., AND KERMIT H. KATZ, M.D., BOSTON, MASS.

PAROXYSMAL ventricular tachycardia is a rare but highly important cardiac disorder which demands prompt, energetic treatment. Unless this abnormal rhythm is stopped, congestive failure eventually supervenes, and leads to a fatal outcome.

Quinidine is by far the most reliable drug in the treatment of paroxysmal ventricular tachycardia. Levine¹ states that atropine may be used as an adjunct to quinidine therapy if the latter alone is not effective. Sampson and Anderson² studied the effects of potassium salts alone in a group of fifty-eight patients with cardiac arrhythmias. Only one of these was a case of paroxysmal ventricular tachycardia. This patient was a thirty-year-old man with premature arteriosclerosis. He was observed during four attacks of paroxysmal ventricular tachycardia which lasted from sixteen hours to five days. Each attack ceased within one hour after the oral administration of a total of two to ten grams of either potassium chloride or potassium acetate.

Since there are very few clinical observations on the use of potassium in the treatment of ventricular tachycardia, we wish to report a gratifying experience with this drug in a patient whose tachycardia was highly refractory to treatment with quinidine and other drugs, but stopped promptly when, in addition, potassium chloride was given orally.

CASE REPORT

A seventy-three-year-old man was admitted to the Fifth Medical Service of the Boston City Hospital on August 23, 1940, with the chief complaint of precordial oppression, palpitation, and wheezing dyspnea of sudden onset twenty-four hours previously. A similar attack, associated with prolonged, severe pain in the anterior portion of the chest, had occurred in June, 1940. Later information from the family physician disclosed that the earlier attack had been caused by coronary occlusion, as proved by an electrocardiogram taken June 31, 1940.

On admission, physical examination revealed a well-nourished, elderly white man with orthopnea and Cheyne-Stokes respiration, but no cyanosis. His heart was considerably enlarged to the left and right. The heart rate was estimated at 208 beats per minute. The heart sounds were distant and of uniform quality. No murmurs or friction rubs were audible. No appreciable effect on the rhythm could be produced by carotid or ocular pressure. The blood pressure was 100/75. The neck veins were distended and the liver was palpated two fingerbreadths below the right costal margin. Moist râles were heard at the bases of both lungs. No peripheral edema was demonstrable.

From the Fifth and Sixth (Boston University) Medical Services, Boston City Hospital, and the Department of Medicine, Boston University School of Medicine, Boston.
Received for publication Feb. 26, 1941.

August 23.—Without the help of the electrocardiogram, it seemed that the cardiac abnormalities on admission were suggestive of paroxysmal auricular tachycardia and congestive heart failure. Therefore, moderately rapid digitalization was started. The only effect was a decrease in the heart rate from 208 to 176 beats per minute.

August 24.—The electrocardiogram showed paroxysmal ventricular tachycardia. Thereupon, digitalis was discontinued and quinidine therapy was started. A total of thirty-three grains of quinidine was given orally in divided doses throughout the remainder of the day. The only effect was a further decrease in the ventricular rate from 176 to 160 beats per minute.

August 25.—Twenty-four grains of quinidine were given orally in divided doses without effect on the ventricular rhythm.

August 26.—The dose of quinidine was increased to forty-eight grains daily (six grains every three hours) and maintained at this level. No change in the ventricular rate was observed.

August 27.—Another electrocardiogram showed persistence of the ventricular tachycardia. The signs of congestive failure appeared to be increasing.

August 28.—Twenty c.c. of a ten per cent solution of magnesium sulfate were injected slowly by vein without demonstrable effect. The electrocardiogram was recorded frequently during this injection.

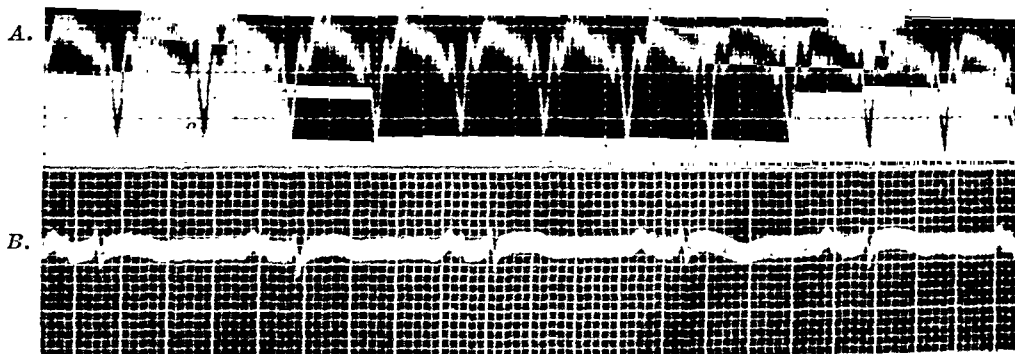


Fig. 1.—Electrocardiograms (Lead II) showing: A, Ventricular tachycardia before use of potassium. B, Normal sinus rhythm after the addition of potassium to the quinidine therapy.

August 29.—Five grains of quinine dihydrochloride were injected intravenously, but no change in the ventricular rate was noted.

August 30.—Five grains of quinine dihydrochloride were given intravenously without effect. One-sixtieth of a grain of atropine sulfate was given intravenously, with electrocardiographic control, without demonstrable change in the ventricular rate and rhythm.

August 31.—Potassium chloride was added to the quinidine therapy in a dose of fifteen grains every four hours. Shortly after the third dose of potassium chloride, the ventricular rate dropped abruptly from 152 to 80 beats per minute.

September 1.—Potassium chloride was discontinued, and the dose of quinidine was reduced to twenty-four grains daily.

September 3.—An electrocardiogram showed normal sinus rhythm and T waves which were more nearly normal than those in the record of June 31.

After the return of the ventricular rate to normal, the signs of congestive failure rapidly disappeared. The patient was discharged, fully recovered, October 31, 1940, on a maintenance dose of 18 grains of quinidine daily.

DISCUSSION

There is considerable experimental evidence to indicate that potassium has striking effects on myocardial function. Sollmann,³ in 1926, working with turtle hearts, demonstrated that potassium in small concentrations exerts a depressant action which affects rhythmicity much more than contractility. Wiggers^{4, 5} and Hoff and Nahum,^{6, 7} working with mammalian hearts, have shown that potassium salts at certain optimal concentrations depress conduction, either locally at the site of direct surface application, or, when given intravenously, in more widespread portions of the conducting system and myocardium. Winkler, Hoff, and Smith⁸ demonstrated striking electrocardiographic changes in dogs after the intravenous injection of isotonic potassium chloride solution. They found that, as the concentration of the serum potassium increased, the following changes occurred: alterations of the T wave; depression of the S-T segments; intraventricular block; disappearance of the P waves; and, finally, cardiac arrest. A comparable study in man, made by Harris and Levin,⁹ showed that an increase of potassium in the blood stream caused:

A. A decrease in the heart rate by virtue of a lengthened diastolic interval (T-P); B. occasional diminution of the height of the P and R waves; and C. occasional, slight prolongation of the P-R and Q-T intervals.

More recently, Thomson,¹⁰ who studied the effects of the oral ingestion of potassium salts on the human electrocardiogram, demonstrated changes in the T waves in fifteen cases and impairment of conduction in two cases out of a total of twenty-four cases. This author is of the opinion that the effect of vagal stimulation and acetylcholine on the heart may be mediated through the action of the potassium ion on the myocardium. Furthermore, Camp (quoted by Thomson¹⁰) has shown that, in dogs, potassium definitely potentiates the vagus action of digitalis.

Not much clinical use has been made of these cardiac effects of potassium. Sampson and Anderson,² as previously mentioned, were able to abolish extrasystoles in many of their cases, and ventricular tachycardia in one case, by giving potassium salts by mouth.

On the other hand, quinidine has been applied generally and successfully in the treatment of certain cardiac arrhythmias. But it is not unusual to find that a frequently reliable remedy may, in an individual case, prove entirely ineffective. The ventricular tachycardia described in this report proved to be refractory to treatment with large doses of quinidine. It further failed to respond to the parenteral administration of certain other drugs, namely, magnesium sulphate, quinine dihydrochloride, and atropine sulphate. Finally, after nine days of continuous ventricular tachycardia despite quinidine therapy, an abrupt change to normal rhythm occurred after the oral ingestion of three grams of potassium chloride.

SUMMARY AND CONCLUSIONS

1. Quinidine alone may be ineffective in the treatment of ventricular tachycardia.

2. Certain adjuncts to quinidine therapy, such as magnesium sulphate, quinine dihydrochloride, and atropine sulphate, may also prove ineffective.

3. Under such conditions, we recommend giving potassium salts in addition to the quinidine therapy. One or two grams of potassium chloride or potassium acetate may be given every two to four hours until a favorable response is obtained.

4. We believe that the action of potassium in our case was specific and not fortuitous for these reasons:

(a) Potassium depresses the conductivity and excitability of the myocardium.

(b) Potassium potentiates digitalis and quinidine.

(c) Potassium alone can abolish extrasystoles and paroxysmal ventricular tachycardia in man.

(d) Lastly, the long duration of the tachycardia, the lack of response to quinidine and other adjuncts, and the prompt response when potassium was added seem to support a cause-and-effect relationship.

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AN UNUSUAL TOXIC MANIFESTATION OF THE ORAL USE OF QUINIDINE SULFATE

REPORT OF A CASE

MELVIN I. STURNICK, M.D.
BOSTON, MASS.

THE toxic manifestations of quinidine and quinine are numerous and well known. Immediate febrile reactions as a result of the administration of quinidine sulfate have not been reported. The case here described illustrates this unusual manifestation of sensitivity to the drug.

REPORT OF CASE

The patient, H. B., a 65-year-old married tailor, was admitted to the Beth Israel Hospital October 10, 1940, because of the sudden onset of shortness of breath. His health had been excellent until four months prior to entry, when he experienced extreme generalized weakness and profuse perspiration while at work. Two weeks later, he developed severe pain in the chest, and a diagnosis of coronary thrombosis with myocardial infarction was made at another hospital. Recurrent substernal pain necessitated readmission to the same institution, but there was no confirmatory evidence of another infarction.

Physical examination disclosed a fairly well-preserved elderly man, with moderate cyanosis of the lips and nail beds. The temperature was 100° F., the pulse rate, 90, and the respiratory rate, 36. The fundi appeared normal except for arteriosclerotic changes. The lungs were resonant and no rales were audible. Examination of the heart revealed the apex impulse in the fifth intercostal space at the left anterior axillary line, a short, blowing, apical systolic murmur, normal rhythm, and sounds of poor quality. The blood pressure was 115/70. The edge of the liver was palpable beneath the right costal margin on deep inspiration; it was not tender. The reflexes were normal.

Urinalyses showed good concentration. One specimen showed a slight trace of albumin. All examinations of the urinary sediment were essentially negative. On admission the erythrocyte count was 5,000,000; the hemoglobin, 105 per cent (Sahli); and the leucocyte count, 12,800; a differential leucocyte count revealed 79 per cent polymorphonuclears, 21 per cent lymphocytes, 8 per cent monocytes, and 2 per cent eosinophiles. Three stools were negative for occult blood. The blood Hinton and Kahn reactions were negative. The icterus index was 6. The non-protein nitrogen content of the blood was 31 mg. per cent. A roentgenogram of the chest, taken soon after entry, showed no parenchymal pulmonary lesion. Electrocardiograms showed left axis deviation, with intraventricular block and a deep S₂, but no definite changes indicative of recent infarction.

Because of the appearance of numerous ventricular premature beats shortly after the patient was admitted, 12 grains of quinidine sulfate were administered daily in four doses. On the fifth hospital day the dose was reduced to nine grains in twenty-four hours. The drug was omitted on the fifteenth day because of tinnitus in the left ear; this subsided within twenty-four hours. The temperature chart from the sixteenth hospital day to the time of discharge is reproduced herewith (Fig. 1),

Received for publication March 11, 1941.

days. At this point it seemed likely that we were dealing with a drug fever. To confirm this suspicion quinidine was again administered on the twenty-eighth hospital day, and all other medication was withheld. As on previous occasions, he was given three grains of the drug at eight A.M., noon, four P.M., and eight P.M. The temperature reached 104° that evening; the drug was discontinued, and the patient became afebrile by four P.M. on the following day. As Fig. 1 shows, this observation was repeated on two more occasions, on one of which the temperature rose to 105°. The leucopenia and splenomegaly did not recur. On each occasion the rise in temperature was accompanied by a corresponding increase in the pulse and respiratory rates. The patient had no other evidences of drug intoxication. He appeared quite well, even during the height of the fever, and complained only of feeling warm. The tinnitus never recurred. Plasma hemoglobin and bilirubin estimations were made before and during the administration of quinidine. There was essentially no change in the plasma hemoglobin, but a slight rise in bilirubin from 0.3 mg. per cent to 0.9 mg. per cent was demonstrated. The plasma hemoglobin was 3.2 mg. per cent before quinidine and 3.6 mg. per cent during its administration.

It is of interest that no febrile reaction resulted from the administration of quinine. The patient was given a total of 25 grains without any effect on the temperature.

SUMMARY

A marked rise in temperature, without other signs of toxicity, occurred repeatedly after the administration of quinidine in doses which are commonly employed therapeutically.

THIRTY YEARS AFTER LIGATION OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

SAMUEL BRADBURY, M.D., GERMANTOWN, PA.

ON APRIL 18, 1909, a woman was admitted to the Pennsylvania Hospital shortly after having been stabbed in the left breast.

A diagnosis of wound of the heart was made, and the operative note, after describing opening the thorax and pericardium, informs us that "the heart was beating regularly and a gush of blood was coming with each systole from a cut about one inch long. A suture of linen thread was passed through the heart muscle, closing this (cut) partially. The blood from the upper end of the wound was bright, and from the lower end, dark. The wound was seen to cross a coronary vessel, and was apparently in the middle of the right ventricle. Five or six linen sutures closed the wound completely."

Actually, the wound crossed the anterior portion of the interventricular groove diagonally from the left above to the right below, about midway between the apex and the auriculoventricular groove, severing the descending branch of the left coronary artery. The patient was in the hospital from mid-April to mid-July, during which time she developed acute pericarditis, empyema, and lobar pneumonia; she was finally discharged "well and strong."

This patient reported to the Pennsylvania Hospital outpatient department October 24, 1940. She is a grandmother, and lives with the daughter, now married, whom she was nursing at the time of the accident. She takes her part in the daily housekeeping activities, climbs the stairs with impunity, and is as well and active as a 75-year-old woman could be expected to be; she presents no subjective symptoms of heart disease.

Examination showed that her blood pressure was 170/85; the pulse rate was 80, the pulse was regular in rhythm but not in force, and the arteries were not particularly sclerotic. The left breast was smaller than the right, and the scar, at the inner margin of the breast, was scarcely noticeable. The cardiac apex was in the fifth intercostal space, 8 cm. to the left of the midline; it was not diffuse and no thrill was felt. The right border of the heart was not displaced. A systolic murmur was heard all over the heart, perhaps best at the base. Expansion of the bases of the lungs was unequal; it was better on the right, where there were râles. There was a drainage scar in the axilla. There was no edema of the ankles or over the sacrum.

A roentgenogram of the thorax, made Feb. 13, 1940, was interpreted as follows: "The heart is not enlarged; there is good pulsation, and no limitation of motion due to the previous operative intervention. The arch of the aorta shows marked calcification. There is calcification of the pleura on the left side. The left half of the diaphragm is slightly elevated, but the diaphragm moves freely and equally on respiration."

An orthodiagram, made April 4, 1940, showed that the transverse diameter of the heart was 11 cm., with a thoracic diameter of 20.2 cm. Also, the heart was described as showing "very slight enlargement, both of the left ventricle and of the right outflow tract."



Fig. 1.

The electrocardiogram (Fig. 1) showed an occasional premature beat, a rate of 88, a P-R interval of 0.14 sec., no axis deviation, inversion of T_3 , and low voltage of QRS in Lead III. The chest lead was normal. Such a curve is not abnormal for a person of this age, and is not diagnostic of heart disease.

This case was reported in 1913 (J. A. M. A., Nov. 15, 1913), four years after the accident. At that time attention was directed to the previously reported cases of wound of the heart, with severed coronary arteries. Three of the patients died soon after operation. Three (the present patient made four) had recovered from their operations; one patient (F. T. Stewart's first case) died of pulmonary tuberculosis and came to autopsy five years after operation.

The present patient is living and comfortable, 32 years after severance and ligation of the descending branch of her left coronary artery. As nearly as we can ascertain, she has no evidence of coronary disease, and she cannot be said to have any cardiac dysfunction.

Abstracts and Reviews.

Selected Abstracts

The Abstracts in this number have been selected from the *Journal of the Mount Sinai Hospital*, New York, 8: 1942, pages 321 to 1176, dedicated to Dr. Bernard S. Oppenheimer on the occasion of his sixty-fifth birthday.

Abramson, D. I.: **Resting Blood Flow and Peripheral Vascular Responses in Different Portions of the Extremities**, *J. Mt. Sinai Hosp.*, New York, 8: 328, 1942.

Certain conclusions can be drawn from the foregoing observations. First of all, since the hand contains arteriovenous shunts which evidently are under the marked control of the vasomotor center, the vascular responses in this region cannot be considered as representative of peripheral blood flow generally. Further, in contrast to the vascular responses in the hand, the blood flow to the normally innervated forearm and leg is more constant, not being diminished, at least, by most noxious stimuli. The arterioles in both types of vascular beds actively dilate for the purpose of heat dissipation, but differ in that those of the hand function under ordinary conditions, while those of the forearm and leg are affected only when the need is excessive. The vascular beds in the forearm and leg, therefore, are more satisfactory than the hand for studying the local effect of sudden changes in the systemic circulation. Finally, they are probably more truly representative of peripheral blood flow as it relates to the metabolic needs of the extremities.

AUTHOR.

Averbuck, S. H.: **Acute Generalized Postoperative Peritonitis Simulating Coronary Artery Occlusion**. p. 335.

The clinical picture of acute coronary artery occlusion may be simulated by many other supra- and infradiaphragmatic syndromes. There is a general awareness of this problem in differential diagnosis. Further emphasis, however, is required in connection with postoperative shock states which are too uncritically ascribed to acute coronary artery occlusion. Two cases of a rapidly spreading postoperative peritonitis accompanied by peripheral collapse and the clinical picture of shock are described. A diagnosis of acute coronary occlusion was made in each instance. Autopsy failed to disclose such a condition in either case. The clinical peculiarities of postoperative coronary thrombosis are commented upon and it is urged that definite confirmatory evidence be sought before making this diagnosis postoperatively in shock states. The value of the preoperative electrocardiogram as a basis of comparison for postoperative records is stressed.

AUTHOR.

Barnes, A. R., and Burchell, H. B.: **The Significance of Negative T Waves in All Three Standard Leads of the Electrocardiogram**. p. 346.

A study of T-wave negativity in all three leads of the electrocardiogram shows that this abnormality may occur in many conditions. T-wave negativity in all three

standard leads associated with upright QRS complexes is an occasional electrocardiographic pattern of strain of the left ventricle. T-wave negativity in all three standard leads may be an electrocardiographic pattern following acute coronary occlusion and if it is associated with a Q pattern the latter probably will be of the Q_3 type. The behavior of the T wave in the chest leads is not predictable when all three standard leads have negative T waves. A number of cases have been encountered with the electrocardiographic abnormality of negative T waves in all three leads, and in which the heart has been believed to be structurally normal.

AUTHORS.

Benjamin, J. E., Landt, H., and Landen, M.: Coronary Disease, Observations on Dispensary Patients. p. 376.

Thirty-six (18 per cent) cases coming to necropsy (1931 to 1941) were found to have myocardial infarction and coronary occlusion. Only four (11 per cent) patients had ever had actual attacks of "cardiac pain." Dyspnea, congestive failure and elevated arterial blood pressure were the outstanding symptoms. The importance of recognizing the picture of coronary obstruction with infarction, as associated with congestive failure only, and not necessarily pain, is stressed.

AUTHORS.

Boas, E. P., and Levy, H.: Angina Pectoris and the Peptic Ulcer Syndrome: Preliminary Report. p. 422.

The authors have presented cases to illustrate the intimate relationship that may be manifested between the symptoms of angina pectoris and those of peptic ulcer. There may be a sudden simultaneous onset of ulcer symptoms and of anginal symptoms. Repeated attacks of angina pectoris at rest ending in coronary thrombosis may occur two to three hours after meals and during the night at the characteristic "ulcer hours." When symptoms of angina pectoris and peptic ulcer co-exist, successful treatment of the ulcer symptoms may cause remission of the anginal syndrome. Epigastric localization of anginal pain may be conditioned by a pre-existing ulcer.

AUTHORS.

Conner, L. A.: The Heart in Fat Embolism. p. 454.

It is evident that in many if not most cases of fat embolism sufficiently severe to be of clinical significance the heart is involved in the embolic process and may play a part in the fatal issue when this occurs. It is doubtful, however, if such heart involvement ever gives rise to symptoms which are sufficiently characteristic to make the clinical diagnosis possible. The large literature on the subject contains no instances of fat embolism which have presented the classical picture of acute coronary occlusion, nor have postmortem studies ever disclosed an authentic example of myocardial infarction as the result of such embolism.

It is conceivable of course that some fragment of fatty tissue larger than the fat droplets might reach the left side of the heart through a patent foramen ovale (paradoxical embolus) and so result in coronary embolism, but no such happening is recorded and such a possibility is too remote to deserve clinical consideration.

The answer, then, to the question posed in the beginning is that there is no support for the view that fat embolism may at times present the clinical picture of coronary occlusion.

AUTHOR.

Crawford, J. H.: *The Diagnosis of Aneurysm of the Heart.* p. 469.

The signs which are most frequently present and appear to be most important in the diagnosis of aneurysm of the heart are: (a) A history of electrocardiographic proof of previous coronary occlusion. (b) The presence of an abnormal precordial pulsation distinctly separated from the apex pulsation particularly when it is situated above the fifth rib. (c) On x-ray examination a localized bulge which cannot be separated from the heart shadow in any view in which it can be seen or an angulation of the left border of the heart. (d) Systolic expansion in the region of the abnormality as seen on fluoroscopy or roentgenkymography is practically conclusive evidence and small or absent contractions in this area are strongly suggestive. (e) Localized pericardial adhesions or calcification of the aneurysmal wall or its contents are also of value when present.

The following conditions simulate aneurysm of the heart closely and must be carefully differentiated from it: (a) Tumor of the heart. (b) Aneurysm of a sinus of Valsalva. (c) Aneurysm of a coronary artery. (d) Calcification of the pericardium. (e) Diverticulum of the pericardium. (f) Loculated pericardial effusion. (g) Cyst of the pericardium.

AUTHOR.

Friedman, B., Jarman, J., and Marrus, J.: *Therapeutic Agents and Renal Implantations in Experimental Hypertension.* p. 534.

Studies of the blood pressure reducing properties of a number of "hypotensive" agents and of tissue implantations in rats with chronic hypertension of renal origin indicate as follows: Erythrol tetranitrate, bismuth subnitrate, allium sativum (garlic extract) and dried kidney tissue (nephritin) are without effect. Potassium thiocyanate in doses which, in proportion to body weight, are about 50 times those advocated for man, produce a slight decline in pressure accompanied by evidences of toxicity. Magnesium carbonate and sulphate are ineffective. An extract of kidney (Page) reduced blood pressure to the normal level during the period of administration of the extract. A fall in blood pressure occurs following subcutaneous implantation of strips of tissue taken from the kidney, liver and spleen. The depressor effect is correlated with the presence of localized necrotic tissue and does not seem to be specific for the kidney.

AUTHORS.

Globus, J. H., and Schwab, J. M.: *Intracranial Aneurysms: Their Origin and Clinical Behavior in a Series of Verified Cases.* p. 547.

A review of the clinical and anatomical features in thirteen cases of intracranial aneurysms led to the following observations: Intracranial aneurysms pre-exist a terminal fatal event by varying lengths of time, in some instances by as many as thirty years and probably longer. In the great majority of instances the life history of an aneurysm is punctuated by two or more explosions characterized commonly by manifestations of subarachnoid bleeding. A fatal issue usually results from the rupture of the aneurysm and extravasation into an area of previously disintegrated brain tissue, ultimately leading to intraventricular hemorrhage. In a few instances death is caused by the effect of the pressure expansion of the aneurysm without its rupture and without tissue disintegration.

Disintegration of brain tissue and hemorrhage into the areas of softening with extension into the ventricles is most commonly encountered in an aneurysm arising from the rostral part of the circle of Willis (anterior communicating, anterior cerebral and internal carotid arteries), while aneurysms of the posterior part of the circles (posterior cerebral, basilar and vertebral), exhibit manifestations of an ex-

panding lesion. Generalized cerebral arteriosclerosis was not common with the aneurysms in this series, there being advanced atheromatous changes in cerebral vessels of two cases, moderate changes in four and none at all in seven instances of our series. This would point, as far as this material is concerned, to the significance of the congenital origin of aneurysms. Syphilitic and mycotic aneurysms were not among this series, indirectly indicating their rarity. The aneurysms were single in all but one case, in which they were multiple. Hypertension was not a frequent accompanying condition, as it was found in only three of the thirteen cases.

The age distribution shows that fatal manifestations of an existing aneurysm usually appear during the third and fourth decades of life, but there is evidence that their silent existence precedes the fatal issue by many years. Aneurysms seem to be evenly distributed between the two sexes.

Clinically the aneurysms occasionally simulate the picture of brain tumor, encephalitis or vascular disorder of a less defined type; signs of increased intracranial tension, however, except headache, were found in few instances, and mainly when the aneurysm was more caudal in location; papilledema was rare; focal signs (often) of localizing character were frequent. Convulsive seizures occurred and, in some instances, had a focalizing value, but when they were concomitant with bleeding into the subarachnoid space, they had no localizing significance. Signs of meningeal irritation when present were indicative of subarachnoid bleeding. The cerebrospinal fluid was often bloody or xanthochromic, indicating recent or older bleeding. Occasionally a high leucocyte count was encountered in the cerebrospinal fluid, leading to the erroneous diagnosis of a septic meningitis. The blood occasionally revealed a leucocytosis, usually found in the course of an episode of subarachnoid bleeding.

AUTHORS.

Goldblatt, H., Braden, S., Kahn, J. R., and Hoyt, W. A.: Studies on Experimental Hypertension. XVI. The Effect of Hypophysectomy on Experimental Renal Hypertension. p. 579.

In agreement with Page and Sweet it has been shown that complete hypophysectomy does not prevent the development of experimental renal hypertension and that it tends to lower slightly the blood pressure of normal animals. In the hypophysectomized animals that did not develop renal excretory insufficiency (the benign phase) the hypertension persisted at high levels for a long time. The malignant phase of this type of hypertension was also observed in an animal that had been completely hypophysectomized. This rules out the hormones of the pituitary body as playing a significant part in the pathogenesis of the arteriolar lesions observed in the organs of animals in the malignant phase of hypertension.

The effect of any surgical procedure, including hypophysectomy, on established experimental renal hypertension must always be evaluated with caution because in some hypertensive animals, even without any type of treatment, there is a tendency for the blood pressure to reach lower levels. It is considered, therefore, that more significance should be attached to the finding that experimental renal hypertension cannot be prevented by hypophysectomy than to the effect of this procedure on previously hypertensive animals.

The results of this study lend no support to the view that the hypophysis plays a significant part in the pathogenesis of experimental hypertension due to constriction of the main renal arteries or of any similar type of human hypertension and offers no justification for surgical or other interference with the integrity of the pituitary body for the treatment of any type of human hypertension that resembles experimental hypertension of renal origin.

AUTHORS.

Harkavy, J.: Vascular Allergy. II Manifestations of Polyvalent Sensitization. p. 592.

Four cases presenting cardiovascular involvement in which capillaries, veins and arteries participated, are reported. Constitutional allergy or atopy was present in three of the four patients. The exciting agents proved to be drugs, tobacco, pollen, foods and bacteria. The various manifestations are regarded as the expression of vascular allergy.

AUTHOR.

Harrison, T. R.: Clinical Syndromes Produced by Temporary Disturbances of the Cerebral Circulation. p. 612.

The foregoing discussion is admittedly incomplete. The author's object has been to consider a group of allied disorders from an illustrative rather than from a comprehensive standpoint. A more complete exposition would have to include other disorders, such as acute mountain sickness, for example. It is probable that in the future new clinical syndromes which fall into the general group of temporary disturbances of the balance between the oxygen supply and the oxygen need of the brain will be described. In any case it would seem that supplementing the usual etiologic and pathologic points of view by attempting a physiologic approach will be helpful in understanding this complex but common and important group of conditions.

AUTHOR.

Hitzig, W. M.: On Mechanisms of Inspiratory Filling of the Cervical Veins and Pulsus Paradoxus in Venous Hypertension. p. 625.

Inspiratory filling of the cervical veins is a nonspecific phenomenon; it occurs not only in chronic constrictive pericarditis, but also in syndromes of venous hypertension (without mediastinitis) such as severe right heart failure (combined type) and superior vena caval obstruction. It is of diagnostic significance in chronic constrictive pericarditis only when it is accompanied by a pulsus paradoxus. The "paradoxical" phenomenon of inspiratory filling of the cervical veins can be demonstrated manometrically by measuring the venous pressure in the veins of the neck. The elevation of the cervical venous pressure in the syndromes studied ranged from $\frac{1}{2}$ to $3\frac{1}{2}$ cm.

Manometric observations reveal that inspiratory filling of the neck veins occurs much more frequently than is clinically suspected. This is due to the fact that pre-existing elevation of the venous pressure interferes with the clinical evaluation of increased distention of the cervical veins during inspiration.

Inspiratory filling of the cervical veins in heart failure represents an imbalance between an abnormally augmented venous return from the abdomen and a diminished right ventricular output. The central venous stasis which surrounds an overloaded right heart retards the venous return from the upper part of the body. This is promptly reflected into tributaries of the superior vena cava, where it causes either visible filling of the veins or manometric elevation of the venous pressure. Inspiratory filling of the cervical veins in superior vena caval obstruction occurs when the circulatory dynamics indicate that the closure is below the azygos vein. In these cases, the inspiratory descent of the diaphragm compresses the inferior vena cava and retards the blood flow through the collateral circulation and the intraabdominal veins.

Paradoxical elevation of the cerebrospinal fluid pressure paralleling the inspiratory rise of the antecubital venous pressure was observed in one case of superior vena caval obstruction. It is suggested that a similar cerebrospinal fluid phenomenon will appear in those "congestive" states which manifest inspiratory filling of the cervical veins (clinically or manometrically).

A concept is proposed in explanation of the genesis of pulsus paradoxus in pericardial effusion. The phenomenon, which may be regarded as a functional exaggeration of normal cardiorespiratory dynamics, will appear when there is a marked discrepancy between the pulmonary blood volume during expiration and the pulmonary vascular capacity during inspiration. This concept can be similarly applied to constrictive pericarditis when the compression is predominantly right-sided and to the "dynamic" forms of pulsus paradoxus associated with laryngeal and intrathoracic tumors.

The mechanical concept of the cause of inspiratory filling of the cervical veins and pulsus paradoxus cannot be ignored in some cases of constrictive pericarditis, but its occurrence in syndromes of venous hypertension (without mediastinitis) favors the cardiorespiratory or dynamic concept.

A "paradoxical pulse" that appears only in certain positions of the arm occurs as a result of abnormal anatomical relations between the subclavian artery and the first rib and the clavicle. The inspiratory weakening of the pulse is localized to the involved extremity in contrast to the generalized "pulsus paradoxus" of cardiopulmonary origin.

AUTHOR.

Krumbhaar, E. B.: A Congenital Cardiac Anomaly: Atresia of Mitral Orifice and Separation of Left Auricle and Ventricle. With an Appended Case of Absent Left Ventricle. p. 737.

A heart of a stillborn infant is reported, in which the left auriculoventricular orifice was obliterated, and the left auricle separated from the left ventricle by a distance of several millimeters. From the diminutive left ventricle, which was connected with the large right ventricle by a small septal defect, a small aorta (?) emerged that communicated with the large pulmonary artery (?) by a widely patent ductus arteriosus. The foramen ovale was widely open. The coronary arteries arose from the large artery. Other congenital anomalies were present, the unilateral ones all being on the left side. The heartbeat was heard before and after delivery, but the child did not breathe or move.

AUTHOR.

Levine, S. A., and Kauvar, A. J.: The Association of Angina Pectoris or Coronary Thrombosis With Mitral Stenosis. p. 754.

A study was made of 38 cases having both mitral stenosis and angina pectoris, 16 of which were examined post mortem. It was found that 17 of 2832 cases of coronary artery disease seen in private practice had mitral stenosis, i.e., 0.6 per cent. These 17 cases of mitral stenosis with angina or coronary thrombosis were observed among 741 consecutive cases of mitral stenosis, i.e., 2.6 per cent.

The incidence of significant coronary artery disease among 314 cases of mitral stenosis examined post mortem was 5 per cent. The average age for the onset of angina was 50.4 years for women and 53.7 for men, the duration of angina being about 4 years in both sexes. Whereas in ordinary cases of angina men predominate about 3 to 1 and die at a younger age, in these cases of angina and mitral stenosis women predominate 2 to 1 and die at a younger age.

Among the 16 cases examined post mortem, the average blood pressure of the women was 175 systolic and 93 diastolic, and for the men 146 systolic and 88 diastolic. The blood pressure for the other cases was somewhat lower.

Seventeen cases had permanent auricular fibrillation. In 5 of the 11 that had congestive failure, angina developed after the initial symptom of dyspnea. Three of the 16 cases examined post mortem showed no significant pathological changes in the coronary arteries. The finding of normal coronary arteries in these 3 cases and

in 9 similar cases reported by other observers indicates that in mitral stenosis factors other than coronary sclerosis may be responsible for the occurrence of angina pectoris. In the great majority of instances, however, when mitral stenosis and angina coexist, the two conditions are independent of each other, the former due to rheumatic infection and the latter the result of ordinary artery sclerosis.

AUTHORS.

Longcope, W. T., Fisher, A. M.: *Involvement of the Heart in Sarcoidosis or Besnier-Boeck-Schaumann's Disease.* p. 784.

In a series of 31 cases of sarcoidosis six patients showed some evidence of myocardial insufficiency during life or sarcoids of the heart and pericardium were discovered at autopsy. In one patient who showed no abnormalities of the heart during life a few lesions were found scattered through the myocardium at autopsy. The remaining five patients presented some evidence of disease of the heart. Three of the patients died. Autopsies performed on two of these cases showed sarcoidosis of the myocardium and pericardium.

The five patients suffered from various degrees of heart failure, often with enlargement of the heart, arrhythmias and electrocardiographic changes.

AUTHORS.

Mann, H., and Mayer, M. D.: *The Uterine Electrocardiogram.* p. 805.

A series of electrocardiograms were taken of a fetus in utero 6 days before a Caesarean operation, of the fetus in utero during the operation, after the uterus had been exposed and of the infant at intervals after birth. Electrodes placed directly on the exposed uterus gave a clear fetal curve without any perceptible maternal deflections. General anesthesia and the operative procedure produced no obvious change in the rate or rhythm of the fetal heart. Changes in the infant's electrocardiogram during the first few weeks are recorded in serial electrocardiograms.

AUTHORS.

Prinzmetal, M., Kayland, S., Margoles, C., and Tragerman, L. J.: *A Quantitative Method for Determining Collateral Coronary Circulation: Preliminary Report on Normal Human Hearts.* p. 933.

A quantitative method for determining the percentage of collateral circulation between the right and left coronary arteries is presented.

This procedure was performed on 12 normal hearts from patients ranging in age from three to sixty-seven years. Collateral circulation was found in all but one; the range being from 0 to 8.6 per cent. The average value obtained was 4.16 per cent. The average flow from the left to the right coronary artery was 19.2 c.c., or 4.55 per cent, of the flow through the left coronary artery, while the average collateral flow from the right to the left coronary artery was 6.2 c.c., or 4.05 per cent, of the flow through the right coronary artery.

The collateral circulation which has been demonstrated between normal coronary arteries, is ready to function immediately when the need arises. If a radiopaque substance, having a viscosity approximately that of blood, is injected into either coronary artery of a normal heart, the entire coronary artery bed is filled, further proving the presence of collateral circulation. If this same radiopaque substance is injected into the anterior descending or the circumflex branch of the left coronary artery of normal hearts, the entire coronary artery tree is filled. It has been shown that collateral vessels are sufficiently wide to permit passage of erythrocytes. This proves the physiologic usefulness of the collateral vessels.

The efficacy of the collateral circulation between the coronary arteries and its branches probably depends not only on the magnitude of the collateral, but also on such other factors as the size of the occluded vessel and the metabolic needs of the ischemic muscle.

AUTHORS.

Robb, J. S., Dooley, M. S., and Robb, R. C.: Displacement of the RS-T Segment by Potassium Chloride. p. 946.

Application of potassium chloride to the surface of the mammalian ventricle does not necessarily cause a greater RS-T displacement than does deep injection.

No support is obtained for the theory that the electrocardiogram is merely the summation of a dextro- and a laevo-cardiogram.

When leads I and III show RS-T deviation in opposite directions the lesion is not necessarily near the septum nor is the lesion necessarily anterior or posterior. When all three standard leads show an RS-T deviation in one direction the lesion is not necessarily limited to one ventricle.

It is again shown that where "injury" is limited to a single ventricular muscle band, a characteristic electrocardiogram results. "Injury" may be of various types, chilling, mechanical blows, pinching, ischemia, undue stretching, or the application of potassium chloride, in fact any agent resulting in the depolarization of a membrane. We have shown that regardless of the type of noxious agent, the result of injury localized to one muscle alone is constant in its effect on RS-T shifts in the electrocardiogram.

AUTHORS.

Schwartz, S. P.: Transient Ventricular Fibrillation: A Study of the Fibrillary Process and Its Development in Man. p. 1005.

An electrocardiographic study was made of the fibrillary process and its mode of development in eight patients who experienced such seizures. These records were compared with those obtained from animals (frogs, rats, dogs, cats and sheep) following faradization of the ventricles, poisoning with drugs or after ligation of the coronary arteries.

The preliminary alterations in the rhythm of the heart that lead to transient ventricular fibrillation consist of (a) an acceleration of the basic ventricular rate during the presence of some form of auriculoventricular dissociation; (b) the onset of "initial" premature beats arising from a constant focus in the ventricles as judged by their persistent similarity; and, (c) the development of short runs of irregular ventricular oscillations which increase progressively in duration and recur from moment to moment.

It appears that these short recurring periods of ventricular irregularities are the "initial" fibrillary periods of the ventricles. They are a distinct and unique feature in man and have not been noted in animals. They invariably foreshadow the appearance of longer seizures. The "initial" premature beats of the ventricles are associated clinically with an effective ventricular contraction which is audible at the apical region of the heart. The "initial" fibrillary periods are associated clinically with progressively diminishing heart sounds for the first 2 or 3 oscillations. The heart sounds disappear entirely after the fourth oscillation and because of the diminished blood supply to the brain, consciousness is lost if they last 20 to 40 seconds. A typical Adams-Stokes seizure with epileptiform convulsions, apnea and incontinence of feces and of urine supervenes if these oscillations last longer than 40 seconds.

The ventricular oscillations that yield these Adam-Stokes seizures are of two distinct types. One type of deflection is uniform in character, rising and falling

evenly to a base line with an amplitude of 8 to 10 mm. and a frequency of 130 to 300 oscillations per minute.

With progressive asphyxia of the heart, the rate may be lowered to 90 per minute. The QRS complexes are continuous with each other so that the T waves are totally absent. This mechanism may be considered as one of ventricular flutter.

The second type consists of irregular oscillations averaging 130 to 460 per minute and varying in amplitude from 3 to 18 mm. in height. They differ in shape, size and form as well as frequency, duration and amplitude from record to record and moment to moment. Periodic waxing and waning of the height of the oscillations may be present and occasionally alternation of the ventricular complexes may be seen. They may persist as long as 6 minutes at one time and as many as 300 periods have been recorded in one patient during 24 hours.

Transient ventricular flutter and fibrillation may be ended by a single premature beat of the ventricles, a succession of these, or a run of ventricular tachycardia. A postundulatory pause, however, invariably precedes recovery.

The auricles maintain their regular rate and rhythm during ventricular fibrillation except in the longer periods when they may be slowed with an irregular rate and at times stand still because of asphyxia.

Except for the frequency and duration and its unusual transient, recurrent and reversible nature associated with profound clinical disturbances, the fibrillary process in man is identical with that in animals.

AUTHOR.

Sprague, H. B.: Syphilitic Aortitis With Aortic Regurgitation: An Electrocardiographic and Autopsy Survey at the Massachusetts General Hospital. p. 1034.

A series of 22 cases of syphilitic aortitis with aortic regurgitation autopsied at the Massachusetts General Hospital from 1926 to 1941 has been analyzed with reference to the electrocardiographic findings. The absence of left axis deviation in the electrocardiogram suggests a complication beyond simple aortic dilatation with involvement of aortic cusps and separation of their commissures. Conditions resulting in acute, or chronically mild strain on the left ventricle, or conditions resulting in an additional strain on the right ventricle appear to be largely responsible for the appearance of a normal electrical axis or a right axis deviation. In cases with bundle branch block, high degrees of coronary obstruction may be present, particularly of the right coronary orifice. But in one case without coronary narrowing, a large aneurysm pressing on and finally perforating into the pulmonary artery was found at autopsy. It is suggested that the electrical axis of the electrocardiogram is of more use than the S-T and T segments in indicating complications of syphilitic aortitis.

The results of this study afford another example of the fact that the extent of disease and the presence of complications are often of more importance than an etiologic factor alone in the production of alterations in the electrocardiogram.

AUTHOR.

Steele, J. M.: Comparison of Simultaneous Indirect (Auscultatory) and Direct (Intra-Arterial) Measurements of Arterial Pressure in Man. p. 1042.

Concerning the comparison of simultaneous measurements of arterial pressure obtained by direct intra-arterial manometry and by indirect auscultatory technique in 39 individuals, it may be said that:

Systolic pressure was underestimated in indirect measurement by about 10 mm. Hg. In the present study, the indirect pressure in the brachial was compared with the direct pressure in the radial artery. This procedure may account for half of this difference.

In auscultatory technique the disappearance of sound proved to be a more accurate measure of diastolic pressure than the sudden muffling. The former overestimated diastolic pressure by 8.8 mm. Hg, the latter by less than one.

The indirect auscultatory method of estimating arterial pressure is, considering its convenience and simplicity, an unusually accurate bedside method.

AUTHOR.

Sussman, M. L., and Dack, S.: The Roentgenkymogram in Myocardial Infarction. III. Cases With Normal Electrocardiogram. p. 1064.

A detailed analysis is presented of 18 cases of coronary occlusion in which the electrocardiogram returned to normal but abnormal ventricular contraction, demonstrated roentgenkymographically, persisted. This indicates the importance of the latter examination in cases in which symptoms of coronary disease or occlusion are present but other objective confirmation is lacking.

AUTHORS.

Wechsler, I. S., and Bender, M. B.: The Neurological Manifestations of Periarthritis Nodosa. p. 1071.

Seven cases of periarthritis nodosa with neurological manifestations are described. The most characteristic nerve disorder in this disease is involvement of single or multiple peripheral nerves in the extremities. The nerves are usually affected individually and at different times. Signs of central nervous system involvement are also present but are never striking, chiefly because gross lesions of the brain or spinal cord in periarthritis nodosa are uncommon. Renal damage and associated arterial hypertension may explain some of the symptoms of brain involvement in periarthritis nodosa.

AUTHORS.

White, Paul D., and Blumgart, H. L.: Cessation of Repeated Pulmonary Infarction and of Congestive Failure After Termination of Auricular Fibrillation by Quinidine Therapy. p. 1095.

Dr. B. S. Oppenheimer, in 1922, in his paper on "Results with Quinidine in Heart Disease," described his experience with two patients who, during the course of auricular fibrillation, had hemiplegia due to emboli. Both subsequently responded to quinidine by a change to sinus rhythm without suffering from a recurrence of symptoms of embolism, either during or after the treatment.

In further development of this same theme, we have herewith reported two patients in whom the administration of quinidine with consequent return to normal rhythm was undertaken despite generally accepted contraindications. This was followed by abrupt and striking improvement, with cessation of pulmonary embolism in Case 1 and of congestive failure in Case 2. In Case 1 the improvement has persisted to the time of writing. In Case 2 quinidine was probably life-saving at the moment, the patient surviving nearly three years before eventual death from his circulatory disease.

AUTHORS.

Wilson, F. N.: Concerning the Form of the QRS Deflections of the Electrocardiogram in Bundle Branch Block. p. 1110.

Multiple unipolar precordial leads have been employed in a large series of cases in which bundle branch block was thought to be present. In the vast majority of instances the use of such leads made it possible to determine whether bundle branch

block was present, and if so, whether the conduction defect was in the right or in the left bundle branch.

A diagnosis of complete bundle branch block should not be based upon the limb leads alone when the QRS interval measures appreciably less than 0.12 second. When the QRS interval equals or exceeds this value, the presence of a conspicuous S deflection in Lead I indicates that the conduction defect is on the right side. The absence of such a deflection indicates that the conduction defect is on the left side.

The position of the heart has a profound influence upon the form of the QRS complex in limb leads. In bundle branch block, the human heart is usually in such a position that the potential variations of the left arm resemble those of the left ventricular surface while the potential variations of the left leg are either small or like those of the right ventricular surface. When the position of the heart is such that these relations are reversed, left branch block may be mistaken for right branch block and vice versa if precordial leads are not taken.

AUTHOR.

Wolferth, C. C.: Relationship Between Biliary Tract Disease and Heart Disease. p. 1121.

Available evidence appears to indicate that the co-existence of biliary tract disease and coronary disease is significantly greater than is to be expected from the incidence of the two diseases. The cause for this co-existence is not clear. There is no good reason at present for believing that coronary disease causes biliary tract disease. Likewise, there is no valid evidence to support the view that biliary tract disease causes coronary disease. It is possible that similar metabolic faults, infections, or errors in the regimen of life may be factors in the production of both conditions but this view, however reasonable, is not as yet supported by actual evidence.

Biliary tract disease and heart disease may under certain circumstances mimic one another. Passive congestion of the liver may be mistaken for gall bladder disease. The anginal syndrome may be simulated by spasm of the digestive tube. It is possible that reflexes from the heart may affect the digestive tract and that reflexes from the digestive tract may affect the heart. Acute coronary occlusion and acute upper abdominal emergencies may furnish difficult problems in differential diagnosis.

The therapy of biliary tract disease may require modification in the direction of conservatism because of co-existing heart disease. Although cardiac symptoms may be improved following surgery on the gall bladder, such improvement occurs in only a minority of cases. Furthermore heart disease adds to the risk of operation. Consequently the presence of heart disease should be looked upon more as a contraindication to operation than as an indication for operation. When, however, biliary tract disease threatens life or causes distressing symptoms, which cannot be controlled by conservative treatment, it may become necessary to accept the risk of operation even in the presence of serious heart disease.

AUTHOR.

Wright, I. S.: Physical Measures in the Treatment of Peripheral Vascular Disease. p. 1128.

An effort has been made to evaluate the present usefulness of various physical measures in the treatment of peripheral vascular diseases. It should be pointed out that these agents represent only a portion of the whole therapeutic picture, which also includes the problems of tobacco, the local care of the lesions and of the extremities, the use of drugs, typhoid vaccine, tissue extracts, alcohol and the

numerous techniques in the surgical field. Anyone purporting to treat these conditions must be thoroughly familiar with the entire field of therapy.

Physical agents are, however, important and it appears well worth while to review their indications and contraindications at this time. Today many of these problems are controversial. The final answers must await the accumulation of further clinical experience and experimental data.

AUTHOR.

Yater, W. M.: Calcification of the Pericardium and Chronic Cardiac Compression: Report and Discussion of Four Cases. p. 1144.

Four cases of calcification of the pericardium have been reported, all showing definite evidence of chronic cardiac compression. It is a relatively rare lesion but is probably always associated with sufficient fibrosis and rigidity of the pericardium to handicap the heart in its function. Ascites is not the constant feature usually thought, and symptoms of circulatory embarrassment may be slight. Partial heart block occurred in two of the cases, auricular fibrillation in two, and right axis deviation in two. Operation is naturally more difficult than in the cases of cardiac compression without calcification. A probable tuberculous etiology existed in one case and a possible tuberculous etiology in two others. In the fourth, no etiologic agent was suggested.

AUTHOR.

Miscellaneous Abstracts

Schroeder, H. A., and Neumann, C.: Arterial Hypertension in Rats. II. Effects on the Kidneys. J. Exper. Med. 75: 527, 1942.

When rats developed cardiac hypertrophy or elevation of blood pressure as a result of one of several methods designed to bring about arterial hypertension, renal vascular disease occurred frequently.

When injury to one kidney was followed by cardiac hypertrophy or elevation of blood pressure, vascular lesions were found with considerable regularity in the opposite one, as well as in the one injured.

Renal lesions rarely occurred in the absence of cardiac hypertrophy or elevated blood pressure.

Renal vascular lesions in rats are occasioned, therefore, by injury to one kidney and are usually associated with, and dependent on, the presence of arterial hypertension.

AUTHORS.

Marvin, H. M.: The Use and Abuse of the Electrocardiogram in Medical Practice. New England J. Med. 226: 213, 1942.

One of the principal reasons the electrocardiographic method is doing widespread harm today is that many physicians overemphasize its value and underestimate its limitations. They confidently expect it to accomplish much the same things that a surgeon expects of an exploratory laparotomy: that it will disclose the nature of the pathologic process, reveal its exact location and extent, and tell a great deal about the immediate treatment and prognosis. They fail to realize that it is purely a laboratory procedure, comparable in many respects with a roentgenogram or a leucocyte count. As such, the electrocardiogram is to be interpreted merely as one finding among many, and in the light of all the clinical evidence and

other laboratory tests. With the exception of the arrhythmias and some cases of acute myocardial infarction, it is reprehensible to attempt an interpretation of the electrocardiogram without knowing the clinical findings and the clinical diagnosis.

AUTHOR.

Harris, A. S., and Moe, G. K.: *Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration.* *Am. J. Physiol.* 136: 318, 1942.

By use of the donor-tagged cell method for the determination of red cell volume in dogs, it has been shown that in the individual dog a linear relationship exists between the red cell volume and the jugular hematocrit over a hematocrit range of from 11 to 57 per cent.

It is suggested that the total plasma volume as determined by commonly employed methods is not necessarily representative of the actively circulating plasma volume.

AUTHORS.

Irvine, A. D.: *Coarctation of the Aorta.* *Canad. M. A. J.* 46: 436, 1942.

Coarctation of the aorta is one of the more rare anomalies of the cardiovascular system. Although present during infancy and childhood it usually does not become manifest till adolescence or early adult life.

The most important change occurring in the vascular system is the development of a collateral circulation between the proximal and distal aortic segments. This is chiefly by the scapular, mammary and intercostal arteries.

Clinically, the condition is diagnosed by the hypertension in the upper portions of the body contrasted with the hypotension in the lower, coupled with evidence of dilated collateral arteries.

Radiologically, the findings of smooth notching in the inferior surfaces of the ribs is pathognomonic. This so-called Rosler's sign is not present in all cases. It is due to the dilated tortuous intercostal arteries which take part in the collateral circulation.

Three cases of coarctation of the aorta discovered accidentally and confirmed by subsequent clinical examination are reported.

AUTHOR.

Book Review

A BIBLIOGRAPHY OF AVIATION MEDICINE: Compiled by Ebbe Curtis Hoff and John Farquhar Fulton, Charles C Thomas, Springfield, 1942, 237 pages, 6,029 entries, \$4.00.

Perhaps it is axiomatic that, in ordinary times, nothing is more tedious or less appreciated than the labors of bibliographers and lexicographers, but the hard work that produced this excellent compilation will surely be rewarded, for the book is timely and comprehensive, and therefore indispensable to workers in its field. Important, also, is the compilers' thorough grasp of the fact that the subject is not new, but has its roots in the work of Boyle, Bert, Torricelli, and Pascal.

The arrangement and indices leave nothing to be desired.

HORACE M. KORNIS.

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American Heart Journal

VOL. 24

NOVEMBER, 1942

No. 5

Original Communications

THE INTERRELATIONSHIP OF DISEASE OF THE CORONARY ARTERIES AND GALL BLADDER

H. R. MILLER, M.D., NEW YORK CITY

FOR half a century, at least, clinicians have insisted that more than an accidental association exists between disease of the heart and of the gall bladder. Three reasons, principally, have been advanced as proof: (1) Anginal pain, and myocardial incompetence, signalized by heart failure, will undergo improvement and disappear upon removing a diseased gall bladder,¹ (2) electrocardiographic abnormalities which are characteristic of the myocardial damage induced by coronary artery disease may disappear after extirpation of a diseased gall bladder,¹ and (3) the concurrence of gall bladder disease and cardiac affections, notably coronary artery disease, is apparently much greater than one would expect, even when due allowance is made for the natural or predictable incidence of the disease in question at various ages.

Although they are suggestive and provocative, these arguments fall short of being wholly convincing; indeed, some of the earliest observers reached their conclusions on the basis of rather flimsy or erroneous suppositions. Nevertheless, the concept of an interrelationship between dysfunction of the gall bladder (or other parts of the bile duct system) and the coronary circulation (or other parts of the cardiovascular apparatus, e.g., the myocardium) will not down; and a similar interdependence may hold for other supradiaphragmatic and infradiaphragmatic organs. We propose, therefore, to discuss clinical, as well as anatomic and physiologic, evidence which may be marshalled to support the hypothesis of a common mechanism. This evidence is furnished mainly (a) by an analysis of the general behavior, the mass excitation, of the autonomic nervous system as a whole, (b) by precise evaluation of the localization and projection of pain, and (c) by recognizing the function of commonly shared afferent pathways which are capable of transmitting abnormally registered pain from one organ to another.²

Presented in Part at Montefiore Hospital in Connection with the Graduate Fort-night, New York Academy of Medicine, October, 1941.
Received for publication March 30, 1942.

To avoid repetition, clinical reports are omitted, except of the concurrence, in two cases, of disease of the coronary and bile duct systems.

I. CLINICAL ASPECTS

1. *Incidence*.—Coronary artery occlusion in association with disease of the gall bladder appears to be on the increase. This has been attributed chiefly to improved methods of diagnosis and to an increase in the number of persons who survive until the fifth, sixth, and seventh decades; the latter factor raises the absolute number of coronary, as well as gall bladder, victims. That progress has been made in diagnosing gall bladder and coronary artery disease cannot be denied, and it is safe to assume that the total number of victims of both disorders has increased since the span of life has been lengthened. Certainly the decades between 40 and 70 years include many patients with coronary and gall bladder disease. In still older people, the very aged, a decreescent state of the tributaries of the heart is frequently found, but many in this group will have very mild or no symptoms at all, and therefore are not to be classified strictly as patients with coronary disease. However, it is to the point that these persons may develop pronounced anginal attacks when, as often happens, gall bladder disease supervenes.

Gall bladder disease in the very old is more frequent than is generally suspected. In homes and institutions for the aged, disorders of the gall bladder in both sexes are not at all rare. The onset may be sudden or slow and insidious, or it may be manifested by painless jaundice. Mild or moderate tenderness in the gall bladder region is sometimes the sole indication. In older persons, as well as in younger, the chronic "grumbling" gall bladder, even if silent for long periods, may continue to give rise to further paroxysms, and this possibility seems to be enhanced when the cardiovascular apparatus becomes affected.

2. *Diagnosis*.—Because the local signs, notably pain and its radiation, are quite characteristic in each disorder, disease of the gall bladder is distinguished without difficulty, as a rule, from disease of the coronary artery system. On the other hand, the clinical aspects of the general reaction may provide no distinguishing clues because disease of the gall bladder or coronary system may induce a common, generalized, autonomic response.

(a) *The General (Autonomic) Reaction*.^{2a, 8}—This consists of sympathetic (adrenergic) and parasympathetic (cholinergic) manifestations. To the former belong shock, cardiovascular collapse with attendant blood pressure changes, prostration, psychogenic disturbances such as marked anxiety, and glycosuria. The cholinergic features, which are more conspicuous with infradiaphragmatic disease, frequently are manifested by bradycardia and other changes in cardiac conduction, meteorism,

undue salivation, and vertigo. Fever, polyuria, disturbance of the sleep-waking mechanism, and leucocytosis are also central autonomic derangements, but they cannot be labelled as sympathetic or parasympathetic.

Any or all of these autonomic reactions are known to accompany sudden involvement of the gall bladder or coronary arteries. As a rule, a vigorous autonomic response is associated with a sudden, explosive process in the gall bladder or coronary artery system, and milder and less extensive autonomic manifestations accompany or follow chronic, "smoldering" diseases of these organs. Yet, in these divergent states, the mechanism and pathways for pain may be quite similar, and, as we shall see, even identical.

(b) *Pain*, especially its reference, is perhaps the single most important guide in differential diagnosis. It is well, however, to re-emphasize that pain need not be the sole or even the chief evidence of either coronary artery occlusion or gall bladder disease. However, when it is present, the pain often furnishes telltale evidence. This is so because each organ, as a rule, will reflect pain into a related dermatomic area.

Difficulties in diagnosis arise when the pain is referred to distant dermatomes which are not directly related to the organ primarily involved. Thus, with an attack of acute cholecystitis the pain may be referred into the cardiac zone of reference, namely, the left pectoral and forearm region; or the pain of acute coronary occlusion may be referred into the right flank. Furthermore, pain which is referred into the right posterior shoulder region may be thought to originate in the gall bladder, and really be due to pericarditis associated with coronary disease.

Acute gall bladder disease (cholecystitis, empyema), acute pancreatitis, sudden perforation of the stomach, duodenum or intestine, and acute generalized peritonitis are abrupt, explosive conditions characterized by pain and general manifestations which again suggest a mass excitation of the entire autonomic system. Bowel obstruction or mechanical obstruction of any hollow structure, such as the ureter or bile duct, extensive infarction of an organ, or thrombosis of large abdominal or thoracic vessels (including the pulmonary), or dissecting aneurysm of the aorta induce pain and associated features which sometimes closely simulate the intense anginal attack of acute coronary thrombosis.*

Although it is a rare occurrence, the pelvic organs, male or female, may engender pain that finds its way to the cardiac region; the reverse of this is also true. Abdominal viscera act in a similar way, and the organs closest to the diaphragm cause the most pronounced effects. For example, no other condition more closely simulates acute coronary

*Gilbert and his associates^{2c, 3} claim that afferent impulses from upper abdominal viscera (gall bladder, stomach) may produce reflex vagal coronary artery constriction, and thus cause anginal pain. It is not clear, however, whether such a reflex will account for all instances of gall bladder or stomach pain referred into the cardiac dermatomes. The principle of "over-lapping" afferent impulses, it seems to me, cannot be excluded (see II).

thrombosis than esophageal herniation. Upper abdominal organs possess a double and full innervation (sympathetic and parasympathetic), and perhaps also a more diffusely developed system of visceral afferent fibers. Organs lower in the celomic cavity are not as well developed in this respect, and this may account for the fact that they rarely act as sources of explosive attacks.

Electrocardiographic evidence, also, may sometimes be quite misleading, in at least one of two ways: acute coronary occlusion may fail to cause electrocardiographic changes in the ensuing week or two, or not at all; or an acute gall bladder attack may be accompanied by electrocardiographic changes which are suggestive of myocardial infarction.

3. *Clinical Groups*.—In a general way, the clinical material which exemplifies the interrelationship between gall bladder and coronary disease falls into three groups.

Group 1 consists of patients who develop acute disease of the gall bladder which simulates acute coronary occlusion, or vice versa. In both cases the general constitutional (autonomic) reaction is likely to be violent and widespread, and practically identical. Differential diagnosis on the basis of the common general reaction therefore will not be possible. Nor will the usual guide with respect to the site and reference of pain be available, for the pain may be transmitted by accessory afferent pathways.

Group 2 comprises patients who develop acute coronary occlusion and gall bladder disease almost simultaneously, or within a few hours or days of each other. This problem is not one of simulation or overflow of manifestations from the organ involved to the other viscus. Two organs are acutely implicated, giving rise to common signs and symptoms. Although it is decidedly less frequent than that of Group 1, this set of circumstances is not rare. Summaries of two illustrative cases are cited.

CASE 1.—L. M., 68 years old, who was in excellent health, was suddenly seized, soon after an evening meal, with agonizing upper epigastric and precordial pain. Shock and cyanosis came on at once, and the cyanosis persisted even when oxygen was administered. During the subsequent four days he had recurrent attacks of severe precordial pain, associated with bloody, frothy sputum; there were also attacks of peripheral, as well as cardiac, collapse, and of transient auricular fibrillation. Despite negative electrocardiographic tracings on the 2nd, 8th, and 16th days, the possibility of coronary occlusion could not be excluded. Five days after the onset of the illness he developed mild jaundice which was at first attributed to pulmonary changes attendant upon infarction. The jaundice steadily deepened, and a tender gall bladder mass became palpable. Fever and leucocytosis continued, and the temperature ranged from 102° to 103° on the tenth day. Surgical opinion held that the primary disease was either acute pancreatitis or acute cholecystitis with cholangitis. Laparotomy revealed acute cholecystitis. The patient succumbed to an attack of heart failure on the following day. Autopsy disclosed recent cholecystitis, extensive recent myocardial infarction, and recent thrombosis high up in the left descending coronary artery.

CASE 2.—H. O., 56 years old, was suddenly seized with intense precordial pain, shock, and fever. Acute coronary occlusion was diagnosed. On the following day, a "suggestive" chill and a temperature of 105° developed; the liver suddenly enlarged until it extended about 2 finger breadths below the free costal margin, and the gall bladder became readily palpable and very tender. Operation was postponed because of the serious cardiac condition. The gall bladder disease subsided gradually, but the features associated with myocardial infarction persisted for about four months. The electrocardiogram ten weeks after the onset of the attack showed a sharply inverted T.

Group 3 comprises patients with chronic disease of both organs or systems. The autonomic reactions with respect to both organs may be almost identical, but the clinical manifestations of the somatic alteration in the organ (or system) may well serve as a reliable basis for differential diagnosis. For example, the train of clinical events in slowly developing myocardial infarction is generally unmistakable from that of cholelithiasis or other causes of obstructive jaundice. However, the respective and characteristic general clinical manifestations may be lacking or minimal. Confusion in diagnosis may then arise, particularly if pain is referred by "overlapping" afferent pathways into atypical dermatomic areas.

Closely allied are certain cases in which there are chronic recurrent manifestations with pain in many organs and related districts of the body. These sufferers are frequently brushed aside as neurotic, or become the unfortunate subjects of repeated and futile operations. They are persons, we strongly suspect, whose afferent conducting pathways are diffuse, thus rendering possible the projection of pain from one viscus into the dermatomic areas of multiple organs.

II. THE MECHANISMS AND ROUTES OF VISCERAL REFERRED PAIN

1. *The Dual System of Pathways Commonly Involved.*—Two independent nerve pathways cooperate in the propagation of referred visceral pain. Impulses of pain, for example, which originate in the heart, coronary vessels, or aorta are transmitted into the upper left thoracic spinal cord segments (T 1 to 4) by corresponding afferent (sympathetic) visceral fibers. At these levels, afferent somatic nerves (the upper intercostals) are brought into action, and these, together with the visceral fibers, function to refer pain into complementary related dermatomes. As is well known, these dermatomes consist of the left infra-clavicular or pectoral region and the inner aspect of the left arm. The reference of pain from organs other than the heart into related dermatomes is accomplished by a similar cofunction of visceral and somatic afferent neurons.

In most persons the visceral afferent neurons converge predominantly upon a limited group of dorsal roots at a particular cord level, and thus come into relation with a corresponding restricted group of afferent somatic fibers. In the case of the heart, the preponderance and convergence of entry is at the levels T 1 to 4 on the left side. For

the gall bladder the levels are approximately T 8 and 9 and perhaps 7, according to Head;⁴ T 9 and 10, according to Kappis⁵ and L  wen,⁶ and on the right side. This rather well-defined concentration of afferent visceral fibers makes it possible for each organ to refer pain which is engendered in it to the related surface zones, and this enables the physician in the majority of cases to recognize the site of visceral pain according to the complementary dermatomes that are implicated. More

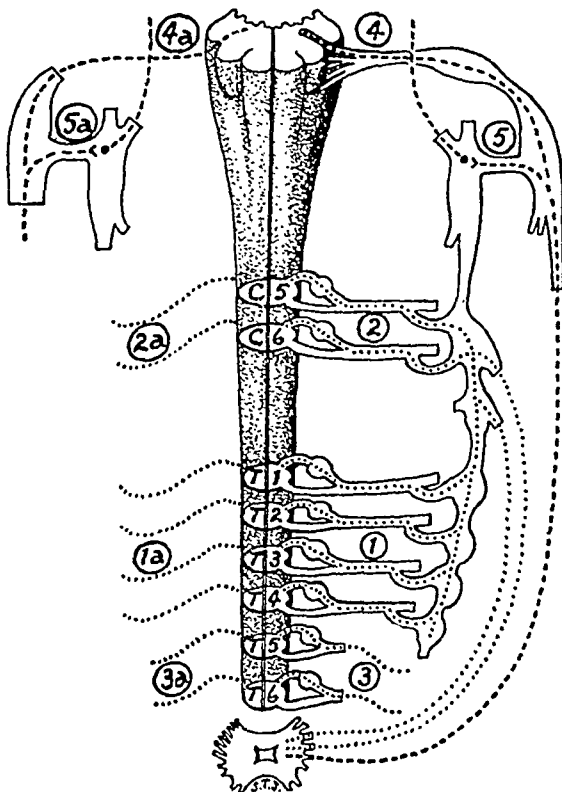


Fig. 1.—(From *Angina Pectoris* by H. R. Miller, Grune and Stratton, New York, 1942. Reprinted by permission of the publishers.) This is a schema of groups of afferent fibers capable of transmitting referred anginal pain. (1) Represents the usual, well-recognized, sinistral group entering the Th 1 to 4 cord segments through corresponding white rami; (1a) is a similar dextral group much less frequently involved. (2) Represents upper left cervical fibers going from upper cervical ganglia to corresponding cervical cord segments; (2a) similar dextral fibers. (3) Represents lower thoracic fibers going from the lower thoracic ganglia to corresponding cord levels; (3a) dextral fibers. (4) Represents the pathway of cardiac afferent fibers in the left vagus destined for the medulla; (4a) a similar pathway on the opposite right side. (5) Represents the pathway of vagal cardiac afferent fibers which ends in the superior cervical sympathetic ganglion; (5a) a similar pathway on the opposite right side. (6) Not included in the drawing is the posterior group of rami connecting the upper thoracic sympathetic chain to the cardio-aortic plexuses. (7) Also not included are the sympathetic fibers from the vertebral plexus, entering the cervical plexus and sending communications to the ansa of Vieussens. The vertebral plexus is generally not accepted as an afferent pathway for cardio-aortic pain.

recently, Ashkenaz⁷ has demonstrated that the gall bladder is connected to the neuraxis by afferent pathways which are far more numerous than we were formerly led to believe, namely, from T 1 to 12, and even lower, on the right side, and from about T 5 to 10 on the left side. The entry of afferent impulses from the gall bladder, which is usually restricted to T 8 to 10 on the right, may therefore readily include many more segmental levels on both sides.

2. *The Participation of Accessory Visceral Afferent Fibers.*—Occasionally, the heart or gall bladder refers pain into an uncommon dermatomic territory. In such cases accessory afferent fibers transmit the impulses of pain into levels of the cord other than those commonly involved—in

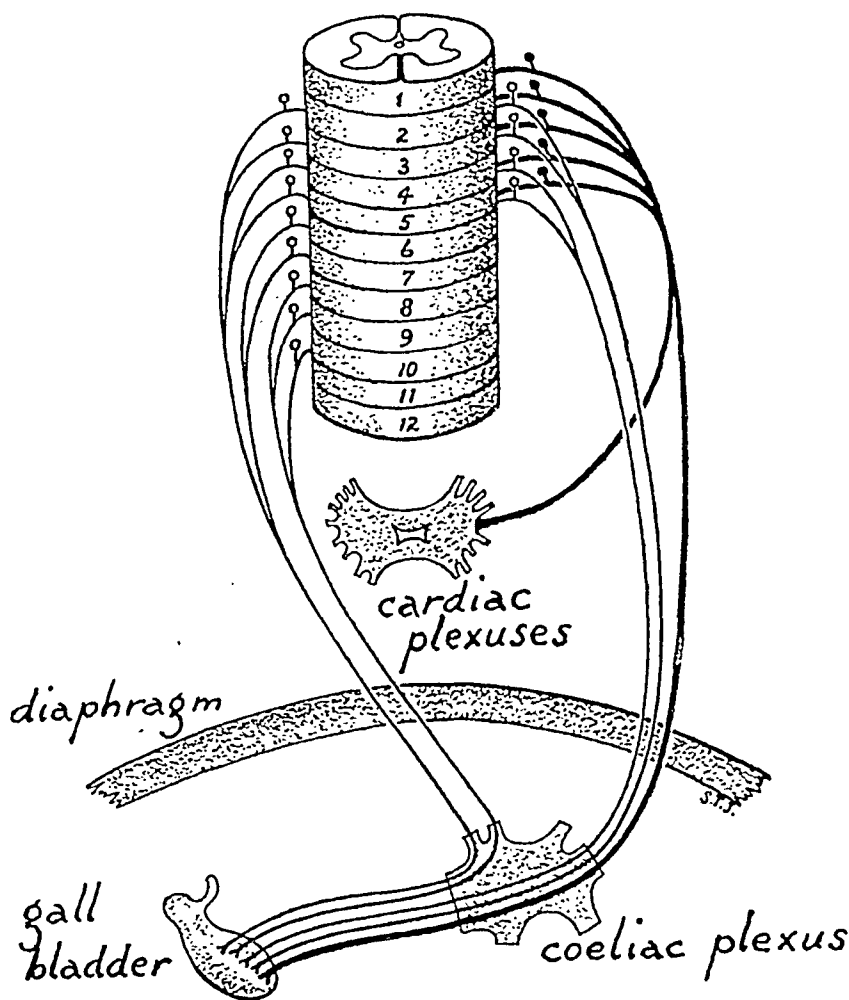


Fig. 2.—The pathways for referred pain from the gall bladder into the cardiac territory. (From *Angina Pectoris* by H. R. Miller, Grune and Stratton, New York, 1942. Reprinted by permission of the publishers.)

The gall bladder has many afferent fibers entering almost every level of the thoracic cord on the right side and a number of upper levels on the left side as well. The cardiac afferent fibers have their usual entry into the upper four thoracic segments of the left side. The radiations of gall bladder and heart disease are, therefore, as a rule, distinctly apart and registered in characteristically different areas of the body. When gall bladder pain is referred into the cardiac territory, we may explain it, on the basis of an arrangement of fibers illustrated above. The predominance of entry of afferent fibers from the gall bladder is indicated as on the *left* side of the upper thoracic cord, the zone in which anginal referred pain is mediated. The same scheme would hold if the mediation were in dorsal ganglia or roots.

other words, outside the zone of the cord which receives the concentration, i.e., the bulk of fibers. Usually, the accessory fibers are too few or too diffuse to carry an appreciable quantity of pain impulses. In certain persons, however, one or more organs may lack a concentration of afferent visceral fibers for any sharply defined segmental zone of the cord.

The arrangement of afferent fibers with respect to any viscus, whether concentrated or diffuse, represents a fundamental anatomic pattern in each case. When this pattern lacks a preponderance of entry into the cord, or when, for some reason, the zone of concentration (the "bottle-neck" in the case of the heart innervation) is interrupted or destroyed, the burden of afferent conduction may be thrown upon the accessory

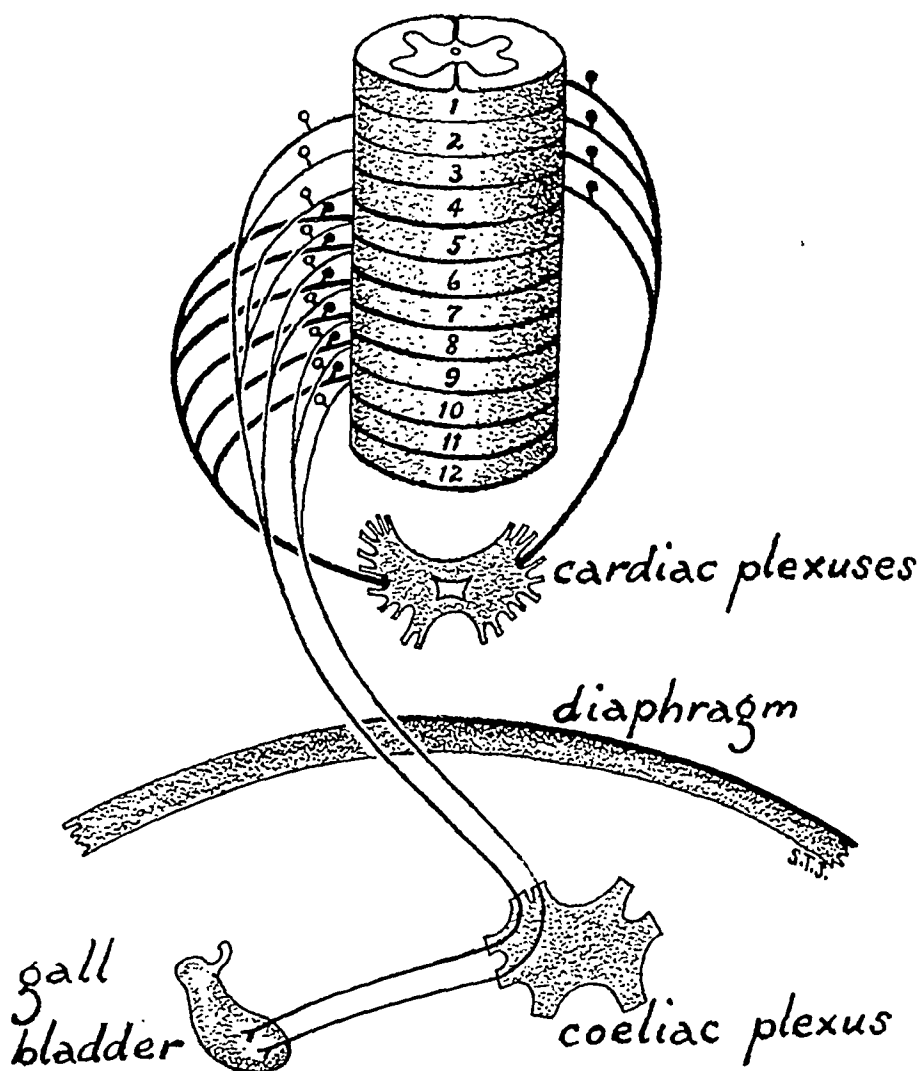


Fig. 3.—The pathways for referred anginal pain into the gall bladder region. (From *Angina Pectoris* by H. R. Miller, Grune and Stratton, New York, 1942. Reprinted by permission of the publishers.)

This drawing illustrates the arrangement of afferent fibers that would prevail in those cases when anginal pain is propagated into the gall bladder region.

The cardiac afferent fibers are drawn here as predominantly *dextral*, and overlapping the entry zone of the main group of afferent fibers from the gall bladder.

groups of fibers. Fig. 1 is a schema of the accessory groups which are concerned with cardiovascular pain, and illustrates the principle that transmission of pain from a viscus can take place by specially concentrated groups of fibers or by diffuse pathways.

This principle of an uncommonly prominent participation on the part of accessory visceral fibers may be invoked to explain the reference of

pain from one organ into the other. For example, when cardiac pain is referred into the dermatomes related to the gall bladder, the reference is by means of accessory fibers which leave the heart and go to cord levels that are concerned with the mediation of gall bladder pain. Conversely, a similar mechanism operates when gall bladder pain is referred into the dermatomic territory which is commonly the recipient of cardiac pain. Figs. 2 and 3 illustrate these mechanisms. A common mechanism accordingly underlies the reference.

CONCLUSIONS

The premise of an interrelationship between disease of the gall bladder and the coronary arterial system rests upon evidence that (1) a common general autonomic reaction is set off in each disorder, and that (2) a common mechanism and afferent pathways are brought into action when the referred pain of coronary occlusion simulates that of gall bladder and bile duct affections, or vice versa.

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AURICULAR FLUTTER ASSOCIATED WITH BIZARRE QRST COMPLEXES

J. SCOTT BUTTERWORTH, M.D., AND CHARLES A. POINDEXTER, M.D.
NEW YORK, N. Y.

AURICULAR flutter is a common and, for the most part, easily diagnosed condition. Clinically, a fast heart rate, with rapid auricular pulsations of the neck veins, serves to make the diagnosis. Electrocardiograms show the regular auricular waves, at a rate of about 300 per minute, which give the base line a characteristic "saw tooth" appearance.

When the auricular flutter, however, is accompanied by changes in the ventricular complexes, it is not as easily recognized in the electrocardiogram. During the past three years several electrocardiograms which showed very fast rates and bizarre wave forms have come to our attention. These were variously diagnosed as nodal rhythm with bundle branch block, ventricular tachycardia, auricular tachycardia, etc. In studying these tracings we have come to the conclusion that many of them are records of auricular flutter with a superimposed deformity of the QRST waves which obscures the auricular flutter waves.

In 1916, White and Stevens¹ reported a case of paroxysmal 1:1 auricular flutter in which, after a very few minutes, aberrant ventricular complexes developed, with subsequent return to normal rhythm. They thought that the aberrant ventricular complexes represented exhaustion of part of the conduction system. An interesting case of 2:1 auricular flutter was described by Cutts and Roberts,² in 1938. In this instance alternate ventricular beats showed a wide QRS complex of the left bundle branch block type. The rhythm eventually returned to normal, with normal ventricular complexes. Gupta and Sinha³ have recorded a case of "auricular flutter with a paroxysmal ventricular tachycardia showing reversion to normal rhythm." From a study of their published tracings we feel that they are more likely examples of auricular flutter with interventricular block. Szekely⁴ reports the case of a 43-year-old man who was suffering from attacks of tachycardia after posterior myocardial infarction. These electrocardiograms are difficult to analyze from the published data, but are very similar to some of the tracings included in this paper.

Recent texts on electrocardiography make little or no reference to auricular flutter associated with block of the ventricular conduction system. Graybiel and White⁵ show two instances, but in each case the

From the Division of Cardiology, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

Aided by a grant from the Frank Melville Fund.

Received for publication Feb. 21, 1942.

deformity of the ventricular complex is insufficient to obscure the flutter wave.

Because we feel that in many instances this type of electrocardiogram may be unrecognized, we are reporting the following cases which are illustrative of the condition.

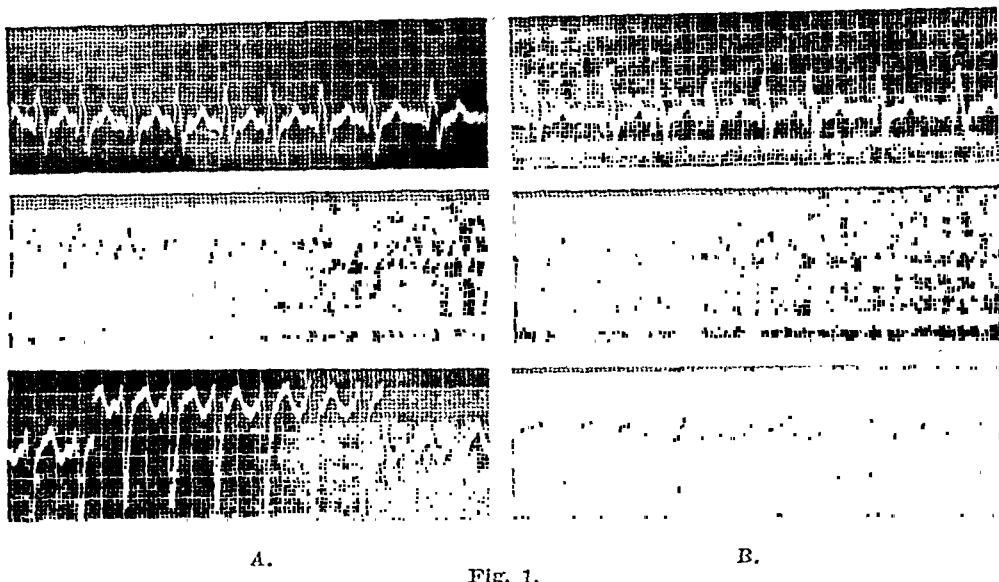


Fig. 1.

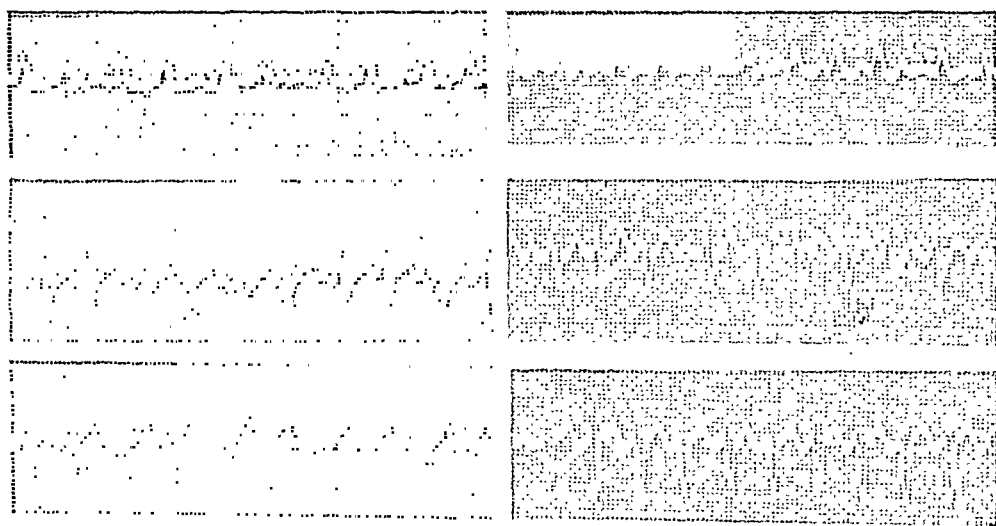


Fig. 2.

CASE 1.—J. L. This 65-year-old man was referred from another hospital for an electrocardiogram (Fig. 1, A). Because we were not certain of the diagnosis, the procedure was repeated one week later (Fig. 1, B). At this time an increase in the A-V block had occurred, and, during these intervals, definite flutter waves could be seen. There was otherwise no change in the second electrocardiogram. Unfortunately, we were unable to trace this patient and nothing is known of his clinical course.

CASE 2.—L. M. This patient was a 67-year-old man. He had suffered from syphilis for many years and a diagnosis of syphilitic aortitis had been made. Prior to 1935 numerous electrocardiograms had been perfectly normal. Fig. 2, A shows

the electrocardiogram during an attack of tachycardia in 1935, and Fig. 2, *B*, a similar attack in 1936. Shortly thereafter the patient died suddenly in his home, and no post-mortem examination was done. We believe that both of these tracings show auricular flutter with interventricular block (left bundle branch block type). There is also a variable degree of A-V block. In Fig. 2, *A* it is rather regular, and alternates between a ratio of 2:1 and 3:1.

CASE 3.—R. L. K. This 67-year-old man was seen shortly after the onset of an attack of tachycardia which followed acute posterior myocardial infarction. Fig. 3 shows the electrocardiogram which was taken during this attack. Fig. 4 shows later

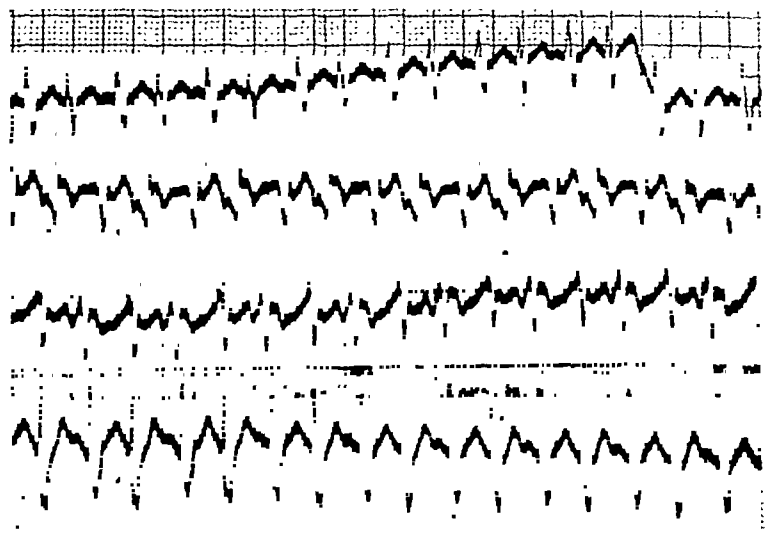
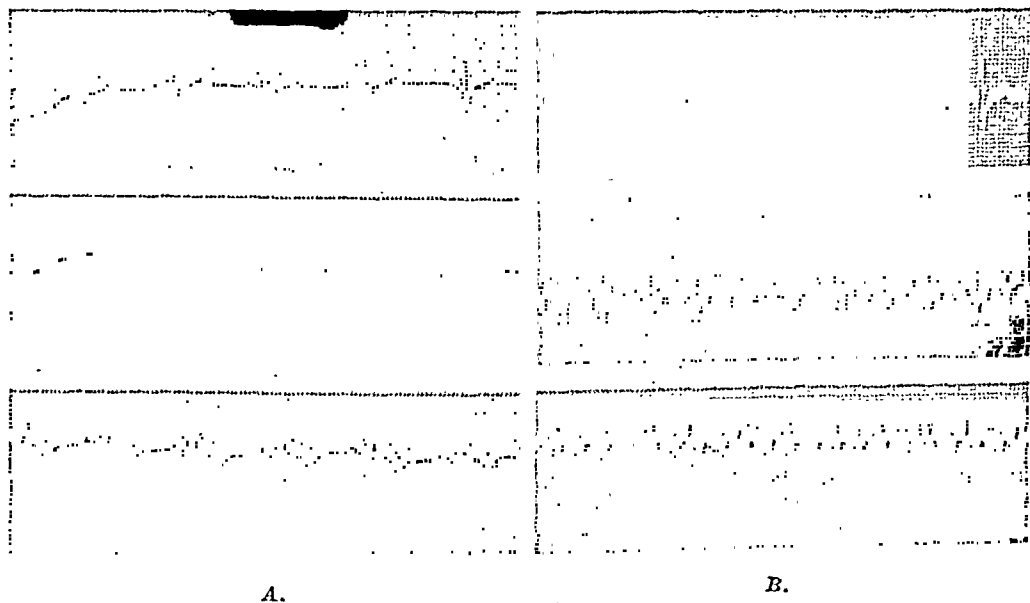


Fig. 3.



A.

B.

Fig. 4.

electrocardiograms on this patient during a period of normal rhythm and during another attack of tachycardia. In the latter case it is obvious that auricular flutter with 2:1 block is present, plus a deformity of the QRS complex. Going back to Fig. 3, one can see the similarity, and it becomes apparent that this is a record of

auricular flutter, with a deformity of the QRS and T waves caused by acute myocardial infarction. This patient has remained well, but continues to have attacks of paroxysmal auricular flutter. The form of the QRS and T remains unchanged.

CASE 4.—J. N. This 56-year-old man was admitted to Welfare Hospital because of chronic pulmonary fibrosis. An electrocardiogram shortly after admission showed (Fig. 5) auricular flutter with a wide QRS complex of the right bundle branch block type. It was only when the 2:1 block increased to 3:1 and 4:1 that the underlying flutter waves could be seen. Repeated electrocardiograms on this patient have shown several interesting changes. The first was a return to normal sinus rhythm, with the same QRS configuration. Then, for a time, the QRS complexes also became perfectly normal, and now the patient again has a right bundle branch block with sinus rhythm.

DISCUSSION

It is clear from the above illustrations that the diagnosis of auricular flutter in the presence of deformed QRS complexes is difficult only when the ventricular rate is rapid. Thus, it is probably a wise procedure in cases of tachycardia to apply carotid sinus pressure while the electro-

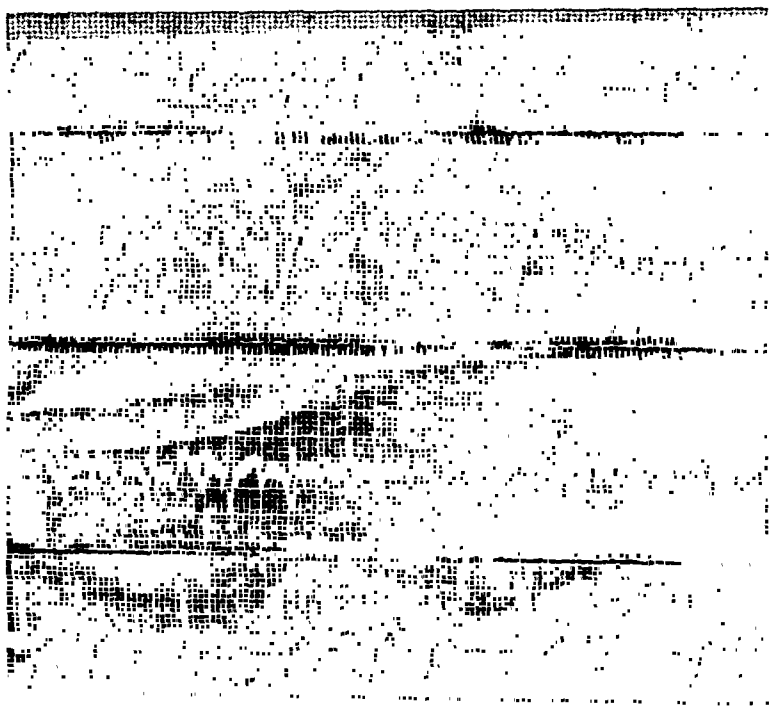


Fig. 5.

cardiogram is being recorded. In our experience, nodal tachycardia rarely, and ventricular tachycardia never, is affected by this form of vagal stimulation. Auricular tachycardias will often terminate, and in auricular flutter the block may be increased sufficiently to reveal definite flutter waves.

Any widening of the QRS complex, with or without marked deformity of the T waves, seems to interfere with the interpretation. Also, the changes in the S-T segment after acute myocardial infarction may cause

difficulty, particularly with posterior lesions, when the changes predominate in Leads II and III, for it is also in these leads that the auricular flutter waves are usually best seen.

As a general rule, ventricular tachycardias show a very constant wave form, whereas tachycardias caused by auricular flutter, with deformity of the QRST complexes, often show variations in the QRST complexes from beat to beat because of interference by the flutter waves. We have also found esophageal leads from the auricular level very helpful in the interpretation of this type of tracing.

SUMMARY

We have called attention to the difficulty of diagnosing auricular flutter in the presence of wide or atypical QRST complexes. In such cases the flutter may be mistaken for ventricular tachycardia. For proper therapy this differentiation is important.

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THE INFLUENCE OF POSTURE ON THE ELECTROCARDIOGRAM

H. S. MAYERSON, PH.D., AND W. D. DAVIS, JR., B.S.
NEW ORLEANS, LA.

FOR a number of years we have been making a comprehensive investigation of the cardiovascular adaptations which accompany the change from the horizontal to the upright position.¹ In most of these experiments the shift in position has been accomplished passively by means of a tilting table; the subject was suspended in such a manner as to eliminate all weight-bearing on the extremities. By thus minimizing the influence of muscular movements in aiding venous return against gravity, the strain on the circulatory system is accentuated and the consequent variations are accelerated. It soon became apparent that the subjects fell into three groups: (a) those who showed an accelerated pulse rate, a rise in diastolic pressure, and little or no change in systolic pressure, and were able to maintain the upright position under these conditions for relatively long periods (twenty minutes or more) without discomfort; (b) those with a more marked tachycardia and rise in diastolic pressure, and often a fall in systolic pressure, who usually fainted within this interval of time; and (c) subjects who, in spite of marked tachycardia, sweating, pallor, and lightheadedness, did not actually faint during the experimental period. A close correlation was found to exist between the level of muscular tone and the ability to maintain the upright position without developing signs and symptoms of syncope.^{1d}

That the electrocardiogram of the normal subject varies with posture is a long recognized fact. Depression of the T wave has claimed particular attention—a phenomenon for which various explanations have been proposed. Recent studies suggest that the alterations in the electrocardiogram in the upright position are caused chiefly by changes in the contact between the heart and neighboring tissues.² There is still the question of the role of anoxemia of the heart muscle as a possible factor.³ Since the tendency to faint, as it occurred in our experiments, was due to cerebral ischemia occasioned by a diminished cardiac output consequent to decreased venous return, it appeared probable that an electrocardiographic study of our subjects might indicate whether or not there was also a concomitant cardiac anoxemia.

Ten healthy adults, students and staff members, whose ages ranged from twenty-one to forty years, served as subjects. Four of these were classified as

From the Laboratory of Physiology, School of Medicine of Tulane University, New Orleans, La.

Aided by a grant from the David Trautman Schwartz Research Fund of Tulane University.

Received for publication March 19, 1942.

"fainters" because they were unable to maintain the upright position for twenty minutes; four showed little or no embarrassment during this period; two were classed as intermediate. The group of fainters included a member of the football team, a former football player, and a former member of the college boxing squad. The usual procedure was to take a control set of tracings with the subject in the horizontal position after a rest of at least fifteen minutes. Each set comprised the three standard leads and Lead IV F. As soon as the control electrocardiograms were completed, the subject was tilted, feet down, to the upright position (75°), and a second group of records was obtained. Four additional sets of tracings usually followed at five-minute intervals; the subject was returned to the horizontal position at the end of about twenty-three minutes. When syncope seemed imminent during this period, tracings were made before the blood pressure fell appreciably. Electrocardiograms were taken as soon as possible after the return to the horizontal position, as well as five and ten minutes later. Except in one instance, each subject was studied on at least two separate occasions.

All records were measured as suggested by Ashman and Hull.⁴ The areas of the tracings were measured planimetrically after the records were projected to a magnification of approximately four times the original size.

RESULTS

P wave.—The changes in P_1 were difficult to evaluate quantitatively because of the normally low voltage of the P wave in this lead, but there appeared to be a trend towards a slight decrease in height, beginning with the assumption of the upright position and continuing until the horizontal position was resumed. The changes in P_2 were much more definite; the voltage usually increased immediately after the subject was tilted. In some experiments the voltage continued to rise, and reached, at the end of about ten minutes, a maximum value which was approximately double that of the control. In other instances, the maximum was not attained until the end of the F. D. (feet down) period. In five experiments, the initial rise was followed by a return to the control level after five or ten minutes; there was no further change during the F. D. period in three cases; in the remainder a secondary rise took place toward the end of the period. The resumption of the horizontal position was succeeded in most instances by a quick return to control voltage values. In one experiment, when the subject was tilted back to the horizontal, there occurred an immediate rise in voltage similar to that observed when he was raised to the F. D. position.

The most striking changes were observed in Lead III, in which tilting produced a marked increase in height in seventeen of the nineteen experiments (Fig. 1). This increase was usually maintained throughout the F. D. period, and the voltage at the end was at least twice that before or after tilting. Two subjects of the athletic type, one a fainter and the other an intermediate, showed a diphasic P_3 in the horizontal position which became more positive when the upright position was assumed. The diphasic character persisted in the two experiments on each subject; in the second case the wave became entirely positive and approached the upper limit of normal voltage (0.20 mv.). In two sub-

jects there occurred a slight retardation of the upstroke of the wave and an acceleration in the speed of the down stroke, producing a scythe-like curve which became more pronounced as the tilting period was prolonged, and disappeared on return to the normal position. In two other subjects who evinced notching of the ascending limb of P_2 when they were in the horizontal position, the notches became more conspicuous during the F. D. period.

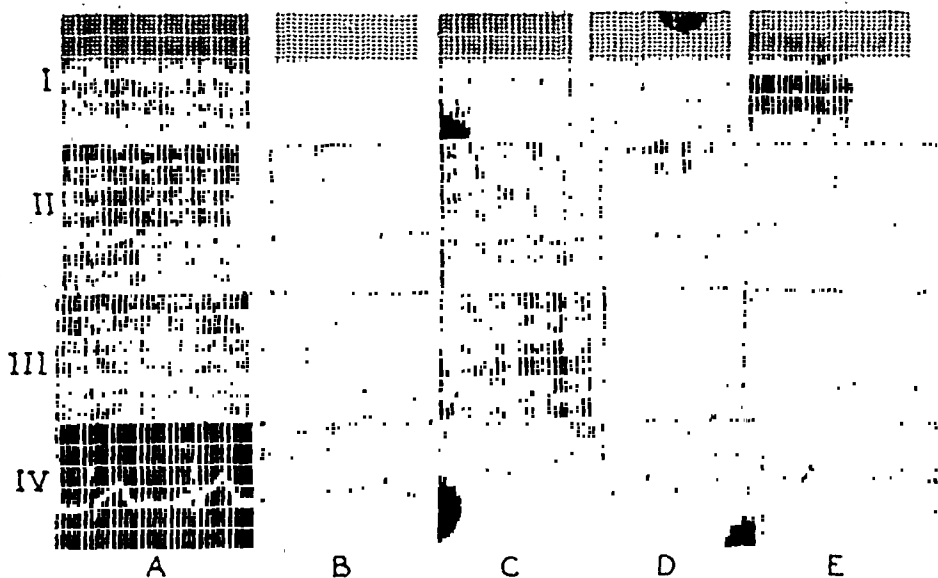


Fig. 1.—Subject J. A. G. Sthenic build. Intermediate. *A.* Control observations in the horizontal position; *B.* $P. = 114/76$; $P. R. = 86$; resp. = 22/min. *B.* Immediately after tilting; *B.* $P. = 124/82$; $P. R. = 107$; resp. = 22/min. *C.* Ten minutes after; *B.* $P. = 118/82$; $P. R. = 111$; resp. = 20/min. *D.* Twenty minutes after; *B.* $P. = 122/84$; $P. R. = 132$; resp. = 22/min. *E.* Control immediately after return to the horizontal position; *B.* $P. = 112/78$; $P. R. = 91$; resp. = 24/min. At *C* subject pale and sweating profusely; at *D* lightheaded.

P-R interval and segment.—Assumption of the F. D. position was accompanied in all but two cases by an immediate and progressive shortening of the P-R interval, amounting, at the end of ten minutes, to 10 to 20 per cent. This change was associated, but not correlated, with a variable and often decided increase in pulse rate. The lack of correlation was particularly evident in connection with the variations on the return to the horizontal position. At this time there was a bradycardia, particularly noticeable in the fainters (Fig. 3), but in only two cases was the P-R interval increased beyond control values.

Changes in the P-R segment were, for the most part, correlated with those in the P waves: a depression of the segment accompanied an increase in P_2 or P_3 . This depression, which may be interpreted as the auricular T wave, was also prominent in those cases in which diphasic P waves were present, and tended to become positive or isoelectric.

QRS complex.—Assumption of the F. D. position, in the majority of cases, resulted in an immediate decrease in the voltage of R_1 and R_4 ,

no consistent variation in R_2 , and an immediate increase in R_3 (Fig. 1). There was little further change during the F. D. position, except that R_1 in the fainters was likely to show an additional, slight decrease. Three of these fainters gave evidence of an immediate, small decrease in R_3 . Four athletic subjects (two fainters and two nonfainters) exhibited slurring or notching of the R waves in one or more leads. With the assumption of the F. D. position these slurs and notches, which often became more prominent, shifted in a counterclockwise direction (Fig. 2), and the shift, in several instances, increased progressively during the F. D. period.

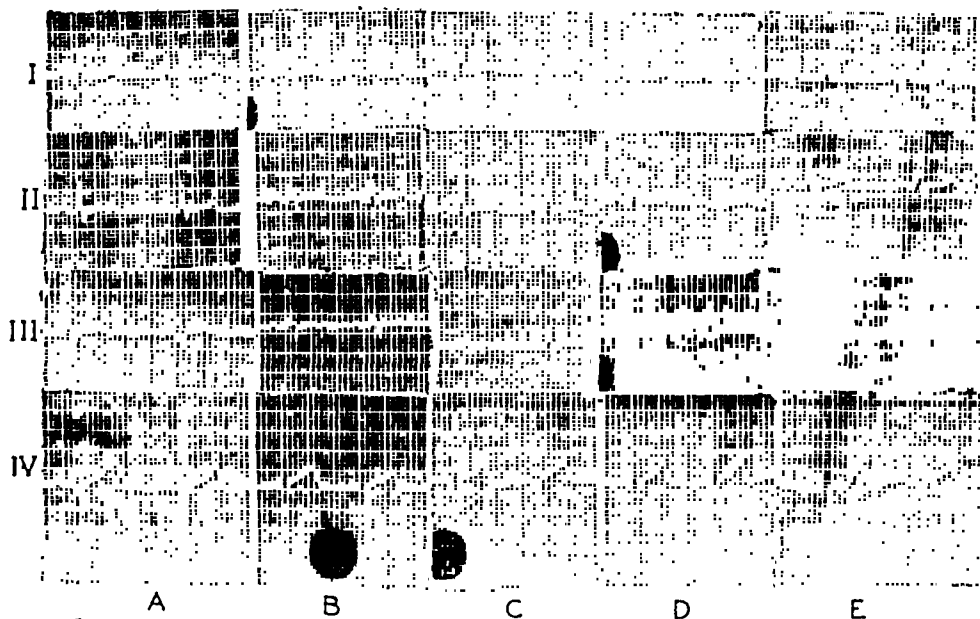


Fig. 2.—Subject T. G. Athletic build. Quarterback on football team. Fainter. A. Control observations in the horizontal position; B. P. = 116/72; P. R. = 72; resp. = 17/min. B. Immediately after tilting; B. P. = 118/78; P. R. = 95; resp. = 25/min., shallow and abdominal. C. Ten minutes after; B. P. = 118/94; P. R. = 98; resp. = 24/min. D. Twenty-three minutes after; B. P. = 103/88; P. R. = 100; resp. = 11/min., very deep. E. Control immediately after return to the horizontal position; B. P. = 122/88; P. R. = 69; resp. = 12/min. Subject dizzy at C; at D showed dry mouth, frequent swallowing, slight twitching; blood pressure sounds difficult to hear. Almost fainted as table was being tilted back to horizontal.

Tilting resulted in a decrease in the height of Q_1 or an increase in S_1 , whereas Q_3 was generally increased and S_3 decreased. With one exception, the fainting subjects revealed an increase in Q_2 ; one subject also showed a rise in S_2 . The changes in S_2 were generally inconsistent; S_4 was usually increased. The net area of QRS in Lead I diminished markedly when the upright position was assumed, and continued to diminish; the values in eight experiments were less than 40 per cent of the control value after fifteen minutes of the F. D. period. No uniform differences were observed in the area in Lead II, although the duration of QRS inclined to diminish. The alterations in Lead III were likewise variable, but, in general, the areas characteristically increased on tilting; in several experiments they were over five times those of the control.

The area of QRS in Lead IV F definitely decreased. Calculation of the mean electrical axis of QRS from the areas in Lead I and Lead II showed deviation to the right in seven of the ten subjects (Fig. 4), no consistent variation in two subjects, and left axis deviation during the F. D. position in one of the fainters.

T wave.—With the exception of two experiments in which there was no change in Lead I, the records showed a striking decrease in the amplitude of the T wave in all leads. T_2 was inverted in four experiments on two subjects (one fainter and one nonfainter), and T_3 was inverted in all but three experiments. In many cases these changes were progressive during the F. D. position (Fig. 3); the T wave remained depressed when the subject was returned to the horizontal position, but increased to greater than normal value five minutes later. This was particularly true in the records obtained from the fainters.

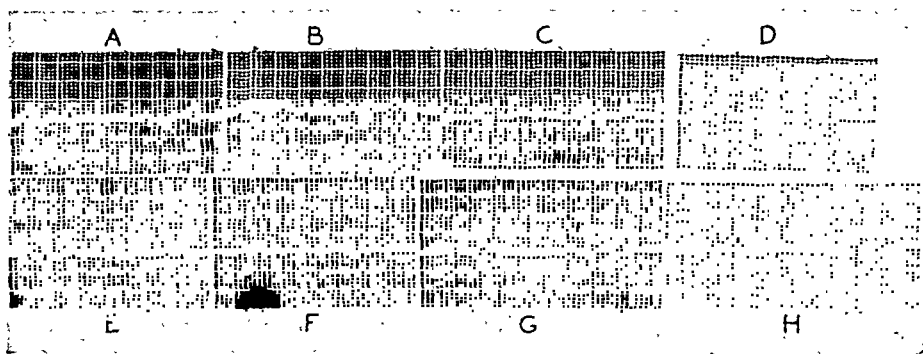


Fig 3.—Subject F. P. C. Sthenic build. Former member of boxing team. Fainter. Lead III. A. Control observations in the horizontal position; B. P. = 122/84; P. R. = 58; resp. = 10/min. B. Immediately after tilting; B. P. = 118/84; P. R. = 68; resp. = 10/min. C. Five minutes after tilting; B. P. = 122/90; P. R. = 72; resp. = 12/min. D. Ten minutes after; B. P. = 126/92; P. R. = 75; resp. = 14/min. E. Fifteen minutes after; B. P. = 120/94; P. R. = 79; resp. = 18/min. F. Twenty-four minutes after; B. P. = 120/110; P. R. = 83; resp. = 16/min. G. Two minutes after return to the horizontal; B. P. = 118/80; P. R. = 57; resp. = 8/min. H. Seven minutes after; B. P. = 120/72; P. R. = 60; resp. = 12/min. Mouth dry, light-headed, at C. At F fine tremors and twitching, particularly at shoulder, profuse sweating and imminent syncope.

In other instances the T waves were still lower than normal five minutes after the return of the subject to the horizontal position. These changes in the T wave were usually accompanied by a depression of the S-T junction which often amounted to more than 0.10 mv. in Leads II and III. There was also a propensity toward shortening of the duration of the S-T segment. With the exception of four experiments, there was a close correlation between the changes in the area and in the amplitude of the T wave. In these cases the appearance of the waves suggested that this was caused by an upward deviation of the S-T segment, which enclosed the same, or a slightly greater, area in spite of the flattening of the T wave. Calculation of the mean axes of the T wave indicated a definite left axis deviation which was much more pronounced than, and in the opposite direction to, the right axis deviation of QRS mentioned above. The difference in the direction of

the axes increased progressively, so that, at the end of the F. D. period, it was often well over 100° (maximum 161.5°) (Fig. 4).

The area of the ventricular complex, QRST, tended consistently to diminish in Leads I, II, and IV F, and changed progressively during the F. D. period in some cases. Two nonfainters uniformly manifested an increase in the area in Lead III, but one gave no evidence of any significant change. The rest of the subjects evinced a definite decrease on being tilted, and a characteristic increase again at the end of ten to fifteen minutes of the F. D. period. Calculation of the mean axes (ventricular gradients) revealed deviations either to the right or to the left; the direction of the shift was roughly correlated with the changes in the QRS and T axes. In those cases in which the T axis changed slightly, the QRST axis was usually prone to shift to the right with the QRS axis; when the T axis varied appreciably in direction, the QRST axis veered to the left.

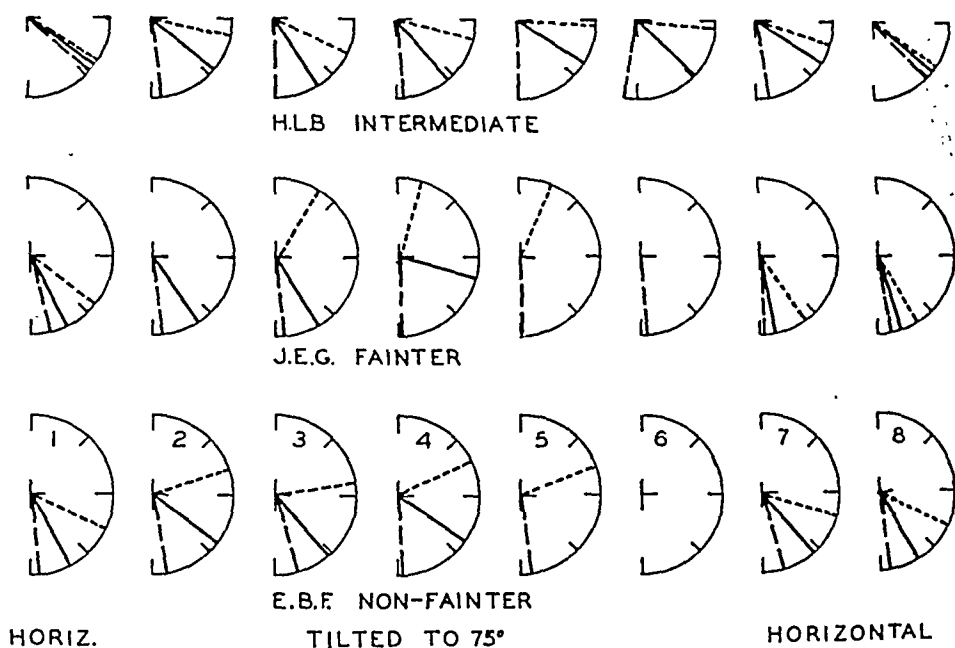


Fig. 4.—Changes in mean axes of ventricular deflections in the upright position. Solid line = average QRST axis (ventricular gradient); dashed line = average QRS axis; dotted line = average T axis. Control values are given in 1; 2 to 6 represent values, calculated from electrocardiograms, taken immediately, five, ten, fifteen, and twenty minutes, respectively, after tilting; 7 and 8 are values immediately and five minutes after return to the horizontal position.

DISCUSSION

The results described above suggest that there are two phases of response to the alteration in posture. When the subject is tilted to the upright position there is an immediate readjustment of the anatomic axis and a consequent reorientation of the electrical fields surrounding the heart. The right axis deviation which occurred in most of our experiments implies an anteroposterior rotation to the right, with a counterrotation to the left around the longitudinal axis.⁵ This rotation

modifies the contacts with neighboring structures,⁶ and may account, in part, for many of the changes, particularly those in the QRS complex immediately after, or soon after, the upright position is assumed. The subsequent variations during the maintenance of this position, however, cannot be explained in this way, for it is improbable that there are any further significant shifts in the position of the heart. These must reflect primarily the response of the cardiovascular system to the influence of gravity.

Among the factors in this response which might conceivably influence the electrocardiographic pattern are a decrease in venous return, changes in the rate and/or depth of respiration, and increased sympathetic activity. Alterations in heart volume do not seem to exert any significant influence, for the changes in the T wave persist after the return of the subject to the horizontal position, when the increased venous return unquestionably results in a larger heart volume. Although the alterations in the form of the T wave during the F. D. period bear a marked resemblance to those caused by the induction of anoxemia in normal hearts of the same age group,⁷ the existence of actual anoxia of the heart muscle is questionable. Our failure to obtain more significant and consistent differences between the fainters and non-fainters, and the relatively quick return to the normal pattern after the subjects were returned to the horizontal position present arguments against this point of view. No correlation was found between respiratory and electrocardiographic changes. On the other hand, some degree of correlation was observed between the increase in sympathetic activity and the electrocardiographic changes. The assumption and maintenance of the F. D. position were usually accompanied by a fall in skin and subcutaneous temperatures, a rise in diastolic pressure, and a tachycardia which was often progressive.^{1b} Fainters frequently showed marked pallor and profuse sweating. Nordenfelt⁸ injected ergotamine into standing subjects and found that the usual postural changes in the electrocardiogram were thereby diminished or entirely eliminated, even though profound circulatory changes, leading to syncope, were taking place. Analysis of our data supports his conclusion that the strong sympathetic stimulation, which occurs as a compensatory response to the diminished venous return and the tendency to cerebral anemia (and anoxia), is a predominant factor in the production of the electrocardiographic deviations brought about by the upright posture.

The changes in the direction of the mean electrical axes indicate that, in addition to changes in conductivity, there are local variations in the excitatory process, and that these are determined by factors which are acting upon the same or different parts of the ventricular muscle with different intensities.⁹ The nature of these factors is unknown, but they may possibly, in these experiments, be associated with the relative increase in sympathetic over parasympathetic activity.

The decrease in the QRST area and the change in the direction of the axes, associated with deviation of the QRS axis to the right, suggest the following explanation of the T-wave changes in terms of the conventional vector analysis.

The QRST area may be regarded as representing a sequence of repolarization which differs from that of depolarization, and/or an independent electrical effect. Theoretically, if the sequence of repolarization is the same as that of depolarization, and if the time course of repolarization is uniform, the net areas, above and below the base lines, of the QRS complex and the T waves must be identical, although opposite in direction, and the area of QRST in muscle of homogeneous properties should be zero. Therefore, a slight shift of the QRS axis to the right, accompanied by a marked decrease of the QRST area, should result in rotation of the T axis to the left, until, with a zero QRST area, the axis of the T wave is in the opposite direction and its area is equal to QRS. In other words, a reduction of the QRST area enables the "true" repolarization T wave to become a larger component of the total T wave and may account for the rotation of its axis to the left.

The correspondence between the theoretical expectation and our actual observations is striking. It suggests that, of the many factors which may influence the electrocardiographic pattern while the subject is in the upright position, the change in the position of the heart and the increased sympathetic activity may be primary.

SUMMARY

Series of electrocardiograms were taken on ten normal subjects before, during, and after passive tilting (feet down) to the upright (75°) position. The outstanding changes were an increase in the amplitude of the P wave in Leads II and III, a decrease in the amplitude of the T wave in all leads, a shift of the average QRS axis to the right and of the average T axis to the left, and a decrease in the QRST area.

It is suggested that the variations which occurred immediately after the assumption of the upright position were the result of a shift in the position of the heart and an alteration in its contacts with neighboring tissues. It is also suggested that, when further changes occurred during the maintenance of the upright position, they were due primarily to the increased sympathetic activity occasioned by the decreased venous return and consequent relative cerebral anoxia.

We are greatly indebted to Dr. Richard Ashman, of the Department of Physiology, School of Medicine, Louisiana State University, for his invaluable assistance in the interpretation of the data and in the preparation of the manuscript. We are also grateful to Mr. Walter J. Trautman, Jr., for his assistance in these experiments.

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THE AURICULAR COMPLEX IN CORONARY THROMBOSIS

NATHAN BLOOM, M.D., AND DONALD GILBERT, M.D.

RICHMOND, VIRGINIA

THERE have been very few investigations of auricular complex changes in acute coronary artery disease. Master¹ observed enlargement of the P wave in his series of cases, and Pardee² implies that acute auricular dilatation may give rise to a large P wave. It is difficult to prove clinically that general cardiac dilatation occurs in acute coronary disease, and therefore it may be only theoretically assumed that local auricular dilatation takes place during the course of acute coronary occlusion. This study is based upon thirty-four cases of acute coronary occlusion which were observed at the Medical College of Virginia, Hospital Division, during the past seven years. In these cases the diagnosis was proved, both clinically and from the electrocardiograms. If an arrhythmia was present at the time of the initial tracing, the case was discarded. An auricular complex less than 0.2 millivolt in height and not more than 0.1 second in duration was considered normal.

In Table I a summary of the normal and abnormal complexes is given. No distinction is made as to the lead in which notching or enlargement of the auricular complex was present. It did occur more frequently in Lead II. In several cases the abnormality occurred in only one or two tracings. It was assumed that these departures from normal were actually due to the acute coronary occlusion, and that reversal to normal took place as the process improved.

In Table II an attempt is made to correlate the observations in these cases. Fifty-nine per cent of the patients had some deviation from normal in the P wave, 33 per cent had a transient or permanent notching of the P wave, and 26 per cent (nine cases) had unusually large, spiking P configurations. The duration of the P wave was within normal limits.

In the nine cases in which there were large auricular complexes, five, or 55 per cent, of the patients died. This was interesting in that the mortality in the cases in which the P waves were normal was only 29 per cent. Three of the patients with normal P waves died within the first twenty-four hours of hospital admission, and it is quite possible that they did not develop P-wave changes because of the short duration of the entire attack. The incidence of arrhythmias and conduction defects was much higher in those cases in which there was some P-wave abnormality, i.e., 27 per cent with notching, and 44 per cent with large P waves, as compared with 7 per cent with normal auricular complexes. Six patients died with arrhythmias or impaired conduction, and this was 75 per cent of the total number which developed arrhythmias.

From the Department of Cardiology, Medical College of Virginia, Richmond, Va.
Received for publication March 25, 1942.

TABLE I
CASES IN WHICH THERE WERE NORMAL P WAVES

CASE	LOCATION OF INFARCTION	DAY	P WAVE	COMMENT
1. Negro female Age 39	?	3	Normal	
		5	Normal	
		6	Normal	
2. White male Age 62	Anterior	1	Normal	
		2	Normal	
		7	Normal	
		21	Normal	
3. White male Age 54	Anterior	1	Normal	
		2	Normal	
4. White male Age 70	Anterior	1	Normal	Hospital death, one day after admission
5. White male Age 68	Anterior	12 hr.	Normal	
		1	Normal	
		5	Normal	
		6	Normal	
		10	Normal	
		17	Normal	
6. White male Age 65	Posterior	1	Normal	
		2	Normal	
		4	Normal	
		15	Normal	
		25	Normal	
7. White male Age 42		2	Normal	
		3	Normal	
		5	Normal	
		41	Normal	
8. Negro male Age 38	Posterior	1½ hr.	Normal	
		4	Normal	
		9	Normal	
9. White male Age ??	Posterior	1 hr.	Normal	Hospital death
		1	Normal	
10. White male Age 55	Anterior	12 hr.	Normal	
		2	Normal	
		6	Normal	
11. White male Age 68	?	1	Normal	Hospital death, one day after admission
12. White female Age 67	Anterior	2	Normal	
13. Negro female Age 59		2 hr.	Normal	
		1	Normal	
		2	Normal	
		13	Normal	
		31	Normal	
		60	Normal	
14. White male Age 68	Posterior	1	Normal	Hospital death, 7th day
		2	Normal	
		5	Impure auricular flutter	
		6	Normal	
15. Negro male Age 37	Anterior	3	Normal	Some signs of pericarditis
		7	Normal	
		9	Notched	
		10	Normal	
		13	Normal	
		19	Normal	
		24	Normal	
		30	Normal	

TABLE I—CONT'D

CASE	LOCATION OF INFARCTION	DAY	P WAVE	COMMENT
16. White male Age 53	Posterior	1 2	Notched Notched	Left hospital 2 days after admission
17. White male Age 51	Anterior	1 2 3 5 8 11 18 31	Notched Normal Normal Normal Normal Normal Normal Normal	
18. White male Age 50	Anterior	1 9 16 2 mo.	Normal Notched Normal Normal	
19. Negro male Age 45	Posterior	1 2 6	Auricular fibrillation Negative Notched	
20. White male Age 51	Posterior	6 hr. 1 4 9	Notched Normal Normal Normal	
21. White male Age 46	Posterior	5 7 13 23 6 mo.	Notched Normal Normal Normal Normal	
22. White male Age 67	Anterior	1 hr. 2 7	Notched Notched Nodal rhythm	QRS 0.12 sec., with nodal rhythm. Hospital death
23. White male Age 60	Anterior	2 17 30 4½ mo.	Normal Notched Notched Notched	
24. White male Age 68	?	4 hr. 7 21 50	Notched Negative Normal Normal	
25. White male Age 62	Posterior	1 4 8 11	Notched Notched Auricular flutter Auricular flutter	Hospital death
26. White male Age 58	Anterior	1 2 10	2.5 mm. 2.5 mm. 2.5 mm.	Complexes low. Returned to clinic 3 months after occlusion, wanting to go to work
27. White male Age 58	?	6 7 11 13 15 27	3.5 mm. 3.5 mm. Auricular flutter 3.5 mm. 3.5 mm. 3.5 mm.	Question as to quinidine intoxication. Arrhythmia stopped on discontinuing drug
28. White male Age 62	Anterior	4 5 6 7	3 mm. 2 mm. 2 mm. Normal	Bundle branch block. Partial A-V and bundle branch block. Hospital death 6/22/39
	Occlusion 4 days on admission			

TABLE I—CONT'D

CASE	LOCATION OF INFARCTION	DAY	P WAVE	COMMENT
29. White male Age 48	Anterior	3	Normal	
		4	3 mm.	
		5	3 mm.	
		6	3 mm.	
		7	3 mm.	
		8	3 mm.	
30. White male Age 62	Anterior	14	2.5 mm.	
		12 hr.	2.5 mm.	
		2	2 mm.	
		3	Normal	
31. White male Age 68	Anterior	4	2.5 mm.	Partial A-V and bundle branch block. Hospital death
		1	3 mm.	
		2	10 sec.	
		3	2 mm.	
32. White male Age 71	?		Normal	Partial A-V block. Hospital death
		1	Negative III	
		3	Normal	
		5	3 mm.	
		7	Normal	
		11	Partial A-V block	
33. Negro male Age 41	Anterior	14	3 mm.	Hospital death
		5	3 mm. high	
34. White male	Posterior ?	7	3.5 mm.	Hospital death
		2	2.2 mm.	
		10	Normal	

TABLE II

I. Total cases	34	33% mortality	
Deaths	11		
II. Patients with normal auricular complexes	14		PER CENT 41
Patients with notching of P wave at variable intervals	11		33
Patients with abnormally large P waves at variable intervals	9		26
III. Deaths with normal P waves	4		29
Deaths with notching P waves	2		18
Deaths with large P waves	5		55
IV. Normal P waves and development of arrhythmia or impaired conduction	1		7 (death)
Notched P waves and development of arrhythmia or impaired conduction	3		27 (2 deaths)
Large P waves and development of arrhythmia or impaired conduction	4		44 (3 deaths)
V. Deaths with arrhythmias or conduction defect	6		75 of total that developed arrhythmias

DISCUSSION

In a small series of cases, departures from normal may have been chance occurrences. We are assuming in our thirty-four cases that the changes in the auricular complexes were significant prognostic factors. Master¹ and Pardee² agree that acute auricular dilatation may give rise to large auricular complexes, and one could assume that, if the acute coronary occlusion was of great enough severity, auricular damage would be more pronounced, and that therefore more deaths could be expected in the cases in which there was evidence of auricular change. The mortality was not increased in those cases in which there was notching or bifurcation of the P waves, although more of these patients developed arrhythmias. Bachmann³ assumed that splitting of the P waves was due to impaired conduction through the interauricular bundle. He demonstrated a conduction bundle extending from the sinoauricular node to the base of the left auricular appendage. Pardee² states that notching of the P waves in one or more leads may be considered normal in about 25 per cent of healthy persons. Nevertheless, after the onset of acute coronary occlusion, it would seem that impairment of the conduction mechanism is added evidence of increased strain on cardiac function.

CONCLUSION

Statistical percentages probably have very little value in a series of thirty-four cases, but we wish to present these two important points that we consider fundamental.

1. Any deviation from normal in the auricular complex, after acute coronary occlusion, is conducive to arrhythmias and impaired conduction.

2. The mortality rate in our series was almost doubled when a large, spiked auricular complex, over two millimeters in height, occurred during the course of the disease.

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THE WELTMANN SEROCOAGULATION BAND IN MYOCARDIAL INFARCTION

JOSEPH H. DELANEY, M.D.,* COLUMBIA, Mo., AND
JOHN W. KEYES, M.D.,† DETROIT, MICH.

INTRODUCTION

CLINICIANS and clinical pathologists are constantly searching for procedures which will aid in the diagnosis and prognosis of various diseases. Specific tests are the ideal, but many of these in the past have failed to fulfill the claims of their discoverers. Nonspecific reactions are frequently of value as diagnostic and prognostic measures. The serum coagulation test, first described in 1930 by Oskar Weltmann,¹ is an example of the latter. This reaction has to do with the effect of certain pathologic conditions on the coagulability of blood serum in the presence of electrolytes. It was applied by Weltmann² as a means of differentiating between obstructive and parenchymatous liver disease and between inflammatory and fibrotic processes. This serum coagulation phenomenon has since been studied by many European investigators,³ and has found a place as a diagnostic and prognostic aid in their clinics. It attracted little attention in America until the past few years. Kraemer⁴ reported his observations in diseases of the liver in 1935. Levinson, Klein, and Rosenblum⁵ made a preliminary report of their study of approximately 1,200 children and adults with a variety of conditions. They called attention to the possibilities of this test and compared the Weltmann reaction with the sedimentation rate. The detailed reports made by them in 1938⁶ and 1939⁷ dealt particularly with the problem of differentiating between active and fibrotic pulmonary tuberculosis. Dees^{8, 9} presented a clinical and experimental study of this reaction in 1940 and evaluated the fundamental factors involved in the phenomenon.

THE TEST

Weltmann¹ observed that normal human serum, diluted to fifty times its volume with distilled water, did not coagulate when heated in a boiling water bath. When tap water was used, or when electrolytes, in the form of the chlorides of calcium, barium, or magnesium, were added to the serum, coagulation occurred upon heating. Inflammatory and exudative processes so altered the serum that coagulation occurred only in solutions containing high concentrations of the electrolytes. Chronic diseases characterized by fibrosis, the healing stages of acute infections, and parenchymal liver damage so changed the serum that coagulation also occurred in the more

From the Department of Medicine, Henry Ford Hospital, Detroit, Michigan.

*Division of Health Education, Stephens College, Columbia, Mo.

†Resident Physician, Cardio-Respiratory Division, Henry Ford Hospital, Detroit, Michigan.

Received for publication March 9, 1942.

dilute solutions. On the basis of these preliminary observations Weltmann devised the serocoagulation test. In principle, the test is carried out by boiling in a water bath equal quantities of serum and graduated concentrations of bivalent electrolytes.

TECHNIQUE

The test is simple to execute, easy to control, and requires little apparatus and material. Simplified modifications and micromethods have been devised.⁹ The following is the standard method described by Weltmann. Ten dilutions are prepared in 500 c.c. quantities from a stock solution of 10% $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$, namely, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, and 0.01%. These dilutions are numbered from 1 to 10, beginning with the most concentrated. Ten small (Wassermann) tubes are placed in a wire rack and also numbered 1 to 10. Into each are pipetted 5 c.c. of the corresponding dilution, and exactly 0.1 c.c. of unhemolyzed serum is added. The tubes are shaken to insure mixing of the contents and placed in a boiling water bath. In fifteen minutes the tubes are removed and examined. The highest dilution producing coagulation is observed. Flocculation, rather than turbidity or opalescence, is read as the end point. The number of tubes in which coagulation occurs determines the coagulation band (C.B.) of that particular serum.

The coagulation band of normal serum regularly extends from the first to the sixth tube. Occasionally, partial flocculation is present in the seventh tube, in which case the coagulation band is $6\frac{1}{2}$. In infectious, exudative, or necrotic processes the coagulation band is shortened or may be entirely absent. This was designated by Weltmann as a "shift to the left." A lengthened band occurs in fibrotic processes and parenchymatous affections of the liver. This has been called a "shift to the right." When exudation and fibrosis occur simultaneously, the coagulation band is the resultant of the balance between the two processes. Thus, lobar pneumonia may produce a coagulation band of 1 or 2. In hepatic cirrhosis the coagulation band is frequently as high as 9 or 10. The coexistence of the two diseases might result in a normal coagulation band.

The fundamental physiologic and chemical factors involved in this coagulation phenomenon are obscure. Dees⁹ pointed out that the literature furnished no definite clue to the physiochemical mechanism which determines the behavior of sera in different diseases. Weltmann¹ demonstrated that the albumin content of the solution is not the controlling factor, and that the ratios of the different serum proteins to each other have no relation to the length of the band. Fibrinogen appeared to play no significant role in the reaction because serum and plasma gave the same values. Klein, Levinson, and Rosenblum¹⁰ found that the albumin-globulin ratio had little effect on the coagulation band. Alterations in the serum pH are reported to exert no demonstrable influence upon the coagulation band.⁷ Dees⁹ demonstrated that serum calcium levels are not the decisive factor in determining the length of the band, even though coagulation failed to occur when calcium was removed from the system in vitro. Calcium administered intravenously tended to prolong the coagulation band temporarily. Clinical condi-

tions characterized by alterations in blood calcium levels were accompanied by no change in the coagulation band.⁹ Dees⁹ suggested that serum lipids are a decisive factor in determining the length of the band. She drew attention to the short band in acute infectious states in which the blood fatty acids are low, and to the long band in anemia, leucemia, nephritis, and diabetes, in which there is an elevation of blood fatty acids.

MATERIAL AND METHOD

Our interest in the application of the Weltmann serocoagulation test to the problem of coronary artery occlusion was aroused by the parallelism between this test and the sedimentation rate and leucocyte count in other conditions characterized by tissue necrosis. Any procedure which could be relied upon to indicate the extent and severity of myocardial infarction would be of value. Several blood studies have already been applied in order to obtain information on this aspect of the problem. White¹¹ pointed out that the degree and duration of the leucocytosis are a useful indicator of the size of the myocardial infarct, and hence of prognostic value. Libman and Sacks¹² stated that leucocytosis is the most frequent significant feature of the condition. In only four of seventy-four cases reported by Levine¹³ was there a leucocyte count of less than 10,000. Coffen and Rush¹⁴ observed an elevation in the leucocyte count in all of their fourteen patients. Hamman¹⁵ stated that the average leucocyte count in this condition is 12,000 to 15,000 and that rarely is the count more than 30,000. Levine¹³ reported one patient who had a count of 34,500, and Hines¹⁶ observed one case in which the total leucocyte count exceeded 10,000 for a period of twelve days. Goodrich and Smith¹⁷ state that, in their entire series of coronary occlusion cases, 35,700 was the maximum leucocyte count. This patient died, and autopsy revealed a large myocardial infarct. Marked leucocytosis usually indicates extensive infarction, and therefore a serious prognosis. Rabinowitz, et al.,¹⁸ observed an increase in the sedimentation rate which was most marked on the third to fifth days, and persisted longer than fever or leucocytosis. Goodrich and Smith¹⁷ studied the filament-nonfilament count^{19, 20} in patients with myocardial infarction and found that it gave information of distinct prognostic value which was superior to that obtained from the total leucocyte count alone.

In applying the Weltmann serocoagulation test in a preliminary way in several cases of myocardial infarction, we were struck by the shortening of the coagulation band. Frequently the "shift to the left" was so marked that flocculation occurred only in tube 1 or 2. It was then decided to follow several consecutive cases with frequent and simultaneous total leucocyte counts, filament-nonfilament counts, sedimentation rates, and Weltmann reactions. The blood specimens were usually

obtained between 9:00 and 11:00 A.M., and only from hospitalized patients. The results of these examinations were charted for each patient in order to compare all procedures. In graphing the Weltmann coagulation band, each square represents one tube of coagulation. The highest eosinophile percentage is recorded. This procedure was followed in twenty-four cases of coronary artery occlusion between September, 1939, and March, 1940. From this series we present twelve representative patients, of whom seven recovered and five died.

The Weltmann reaction has been studied in other cardiac conditions. The coagulation band is shortened in acute rheumatic fever^{9, 10} and lengthened in cardiac decompensation.^{10, 21} Several months after the completion of our observations, we found that Teuffl,²¹ in Germany, had studied the same problem. He reviewed 27 cases in 1936 and added to these in 1937, but did not compare the various procedures which we employed. Our own work is entirely independent of Teuffl's observations. We have found no similar studies in the English, French, or American literature.

CASE REPORTS

CASE 1.—(Chart I) H. A., a white man, aged 76 years, with a past history of angina pectoris, was admitted to the hospital on the day of onset of severe substernal pain. The electrocardiogram indicated posterior myocardial infarction. The coagulation band was 8 on the second day, and fell to 4 on the eighth day. Non-filament counts and sedimentation rates were elevated, but returned to normal as the patient improved and healing occurred. Eosinophiles gradually rose from 1 per cent on the fifth day to 21 per cent on the twenty-third day.

Four and one-half months later he was readmitted, twelve hours after a recurrence of the substernal pain. He was cyanotic, in shock, and remained in extremis four days, when he died of myocardial insufficiency. Again the Weltmann coagulation band progressively fell from an initial 8. Fibrosis and myocardial insufficiency probably combined to prevent further shortening of the coagulation band during both attacks. Only 1 per cent eosinophiles appeared during this attack.

Autopsy showed many areas of myocardial fibrosis and softening, as well as a diffuse area of infarction in the posterior ventricular wall. Neither coronary artery thrombosis nor complete occlusion was demonstrated, although there were many points of marked narrowing as a result of atherosclerosis and calcification.

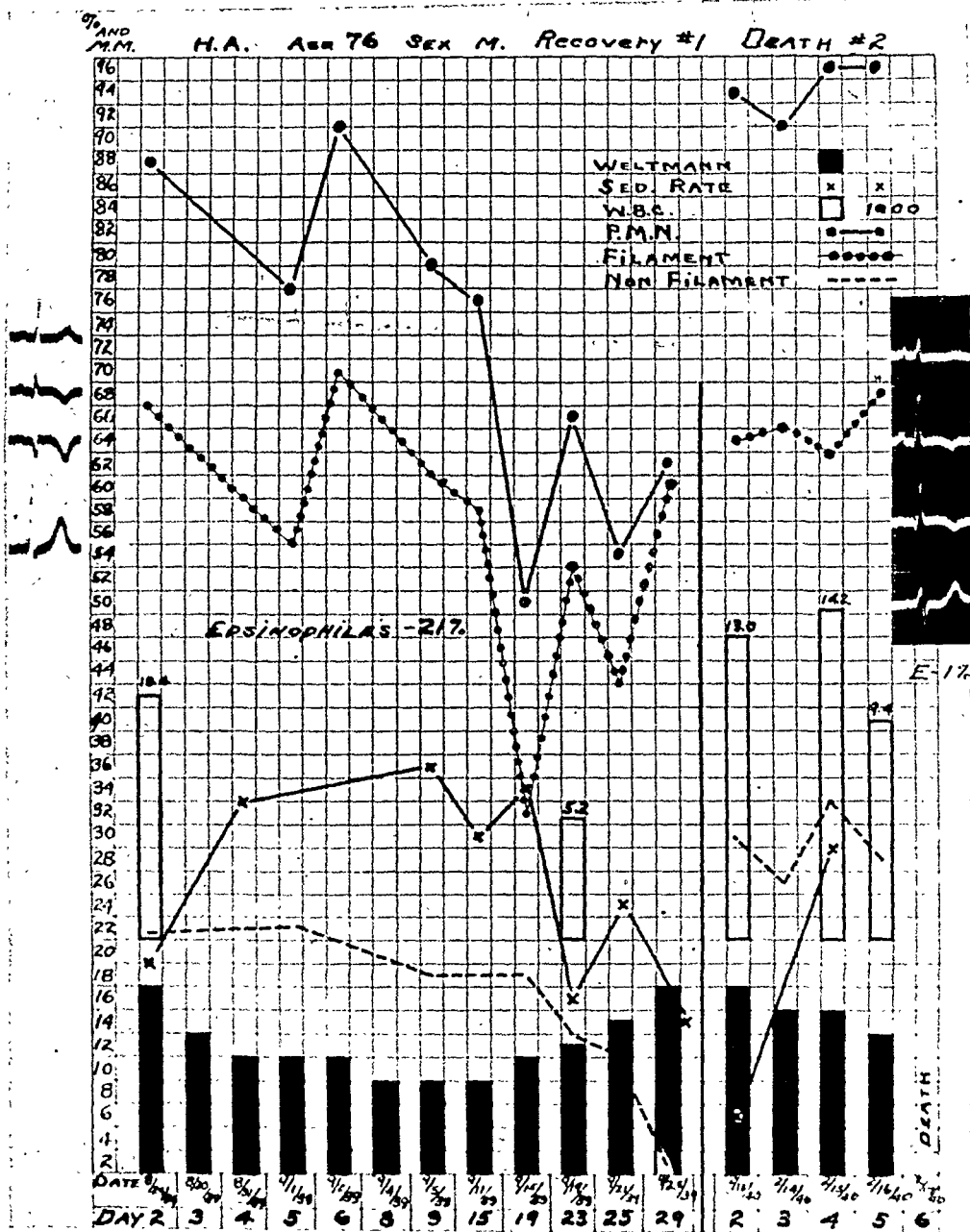
CASE 2.—(Chart II) D. B., a white man, aged 53 years, was admitted Oct. 20, 1939, five days after the onset of substernal pain. Clinical and electrocardiographic observations indicated myocardial infarction. Diabetes mellitus and acidosis were discovered and controlled. The falling coagulation band (from 6½ to 1½) and its persistent shortening, the increased nonfilament count, and the absence of eosinophiles indicated a poor prognosis. A decrease in the leucocytosis and in the sedimentation rate pointed to improvement. Repeated exacerbations of distress and shock occurred, and the patient suddenly died on the twenty-first day of his illness.

At autopsy the heart was enlarged, dark red in color, and covered by a shaggy, fibrinous exudate. A large area of recent infarction involved the posterior left ventricular wall from base to apex, and extended into the interventricular septum for one-half of its width.

CASE 3.—(Chart III) C. D., a white man, aged 46 years, was admitted to the hospital three days after the onset of epigastric and precordial pressure pain.

Clinical and electrocardiographic observations indicated myocardial infarction. The fall in the coagulation band from 4, on admission, to $1\frac{1}{2}$, the upward trend of the nonfilament count, and the elevated sedimentation rate pointed to a poor prognosis. Decreasing leucocytosis and this clinical course indicated improvement. He was found dead in bed on the twelfth day of his illness.

Necropsy revealed that the pericardium was filled with blood. In the anterior ventricular wall there was a large infarcted area which bulged forward with a hemispherical contour. Near the center of this aneurysm a large vertical tear was found. The descending branch of the left coronary artery was very atherosclerotic and almost completely occluded near the ostium.



CASE 4.—(Chart IV) R. J., a white man, aged 65 years, was admitted to the hospital nine hours after the onset of substernal pain. Clinical and electrocardiographic data indicated acute coronary artery occlusion. He grew steadily worse; myocardial insufficiency developed, and he died of general cardiovascular collapse on the third day of the illness. The shortening of the coagulation band from 6 to 4, the elevated sedimentation rates and nonfilament counts, and the absence of eosinophiles were all consistent with the outcome.

The autopsy, limited to the thorax, revealed a greatly hypertrophied heart. The coronary vessels were markedly sclerotic, and a fresh thrombus occluded the posterior

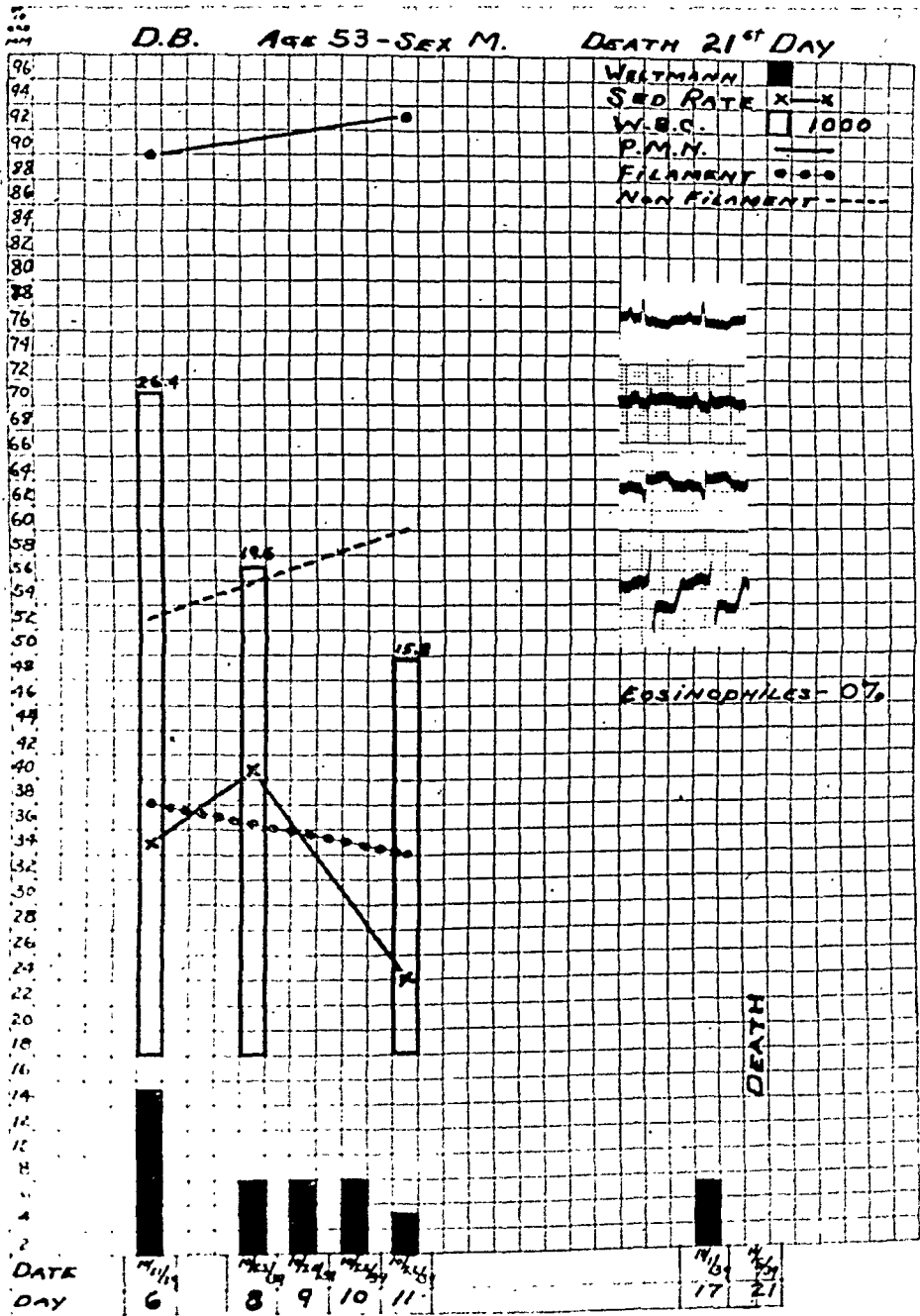


Chart II.—Pronounced "shift to the left," or shortening of the coagulation band in a case of severe infarction. Death on the twenty-first day. The sedimentation rate fell, indicating improvement.

CASE 5.—(Chart V) R. H., a white man, aged 48 years, was admitted to the hospital two hours after the sudden onset of severe epigastric pain, nausea, and vomiting. The differential diagnosis rested between acute coronary artery occlusion and perforating peptic ulcer. An electrocardiogram indicated myocardial infarction. The patient did not do well, developed myocardial insufficiency, and died on the thirteenth day of his illness after a recurrence of the chest pain.

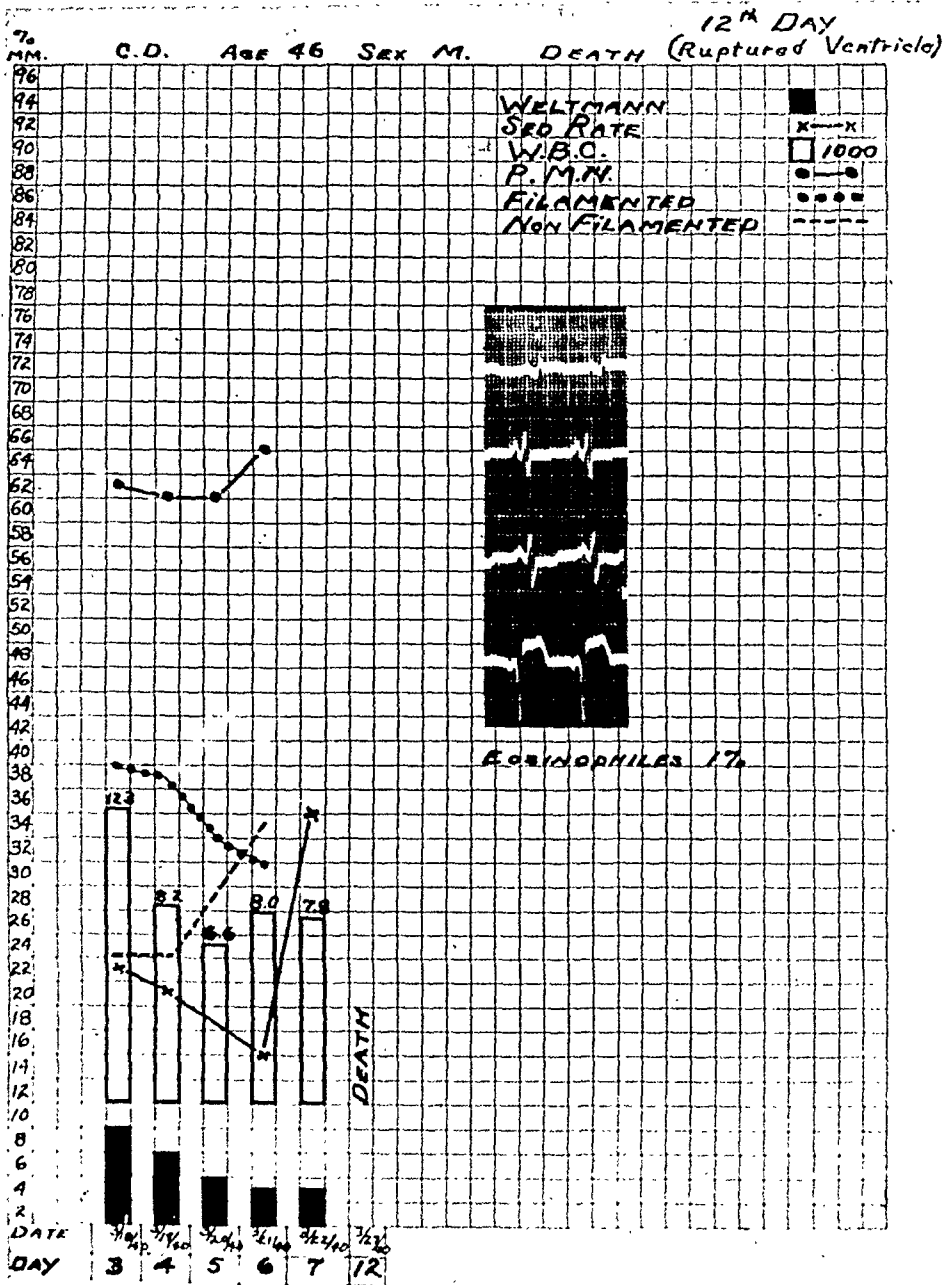


Chart III.—Another case of severe infarction, with a very short coagulation band; death resulted from ruptured ventricle.

In this case, the high leucocyte count, absence of eosinophiles, and rising sedimentation rate were more consistent with the clinical picture and outcome than were the nonfilament counts and the Weltmann reaction. Congestive heart failure undoubtedly prevented a more typical shortening of the coagulation band.

Autopsy disclosed infarction of the anterior wall of the left ventricle, the inter-ventricular septum, and the posterior wall of the right ventricle. Each ventricular cavity contained a mural thrombus. The left coronary artery was markedly narrowed by atherosclerosis.

CASE 6.—(Chart VI) C. A., a white man, aged 54 years, who had had arterial hypertension for many years, first noted substernal pressure August 26, 1939, after

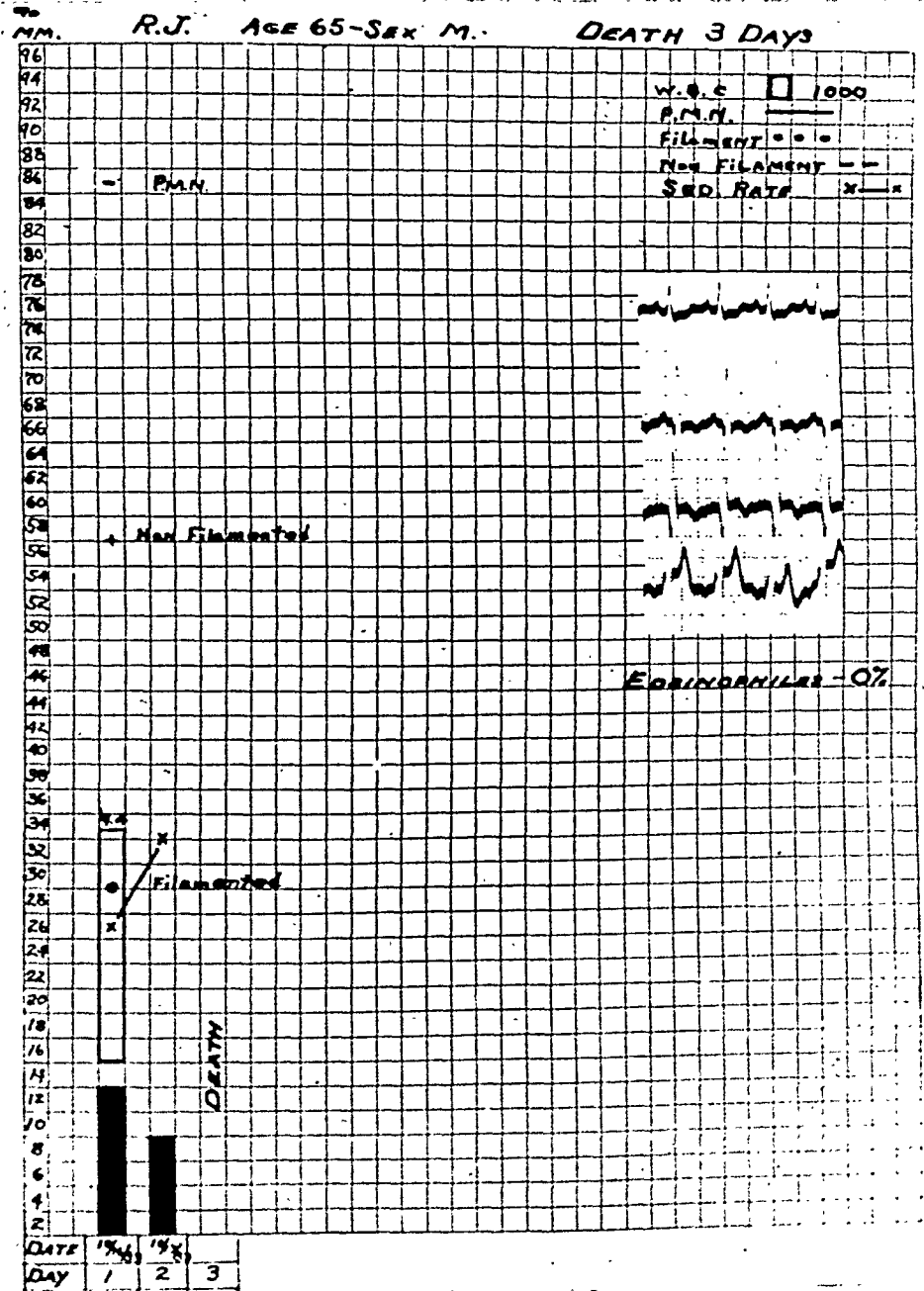


Chart IV.—Showing shortening of the coagulation band, high nonfilament count, rising sedimentation rate, and absence of eosinophiles.

a light breakfast. The distress radiated to both sides of the chest, and was relieved after five minutes by eructations, rest, and "Bisodol." During the next few days seven similar attacks occurred, all related to meals or exertion. On admission to the hospital, August 30, a diagnosis of angina pectoris or impending coronary artery occlusion was made. Since there were no significant changes in the electrocardiogram, Weltmann coagulation band, leucocyte count, nonfilament count, or sedimentation rate, it was felt that infarction had not occurred. Rest in the hospital resulted in a decrease in blood pressure and relief from the attacks. On September 2 he again experienced substernal pain which finally required morphine for relief. Electrocardiographic changes and shortening of the coagulation band,

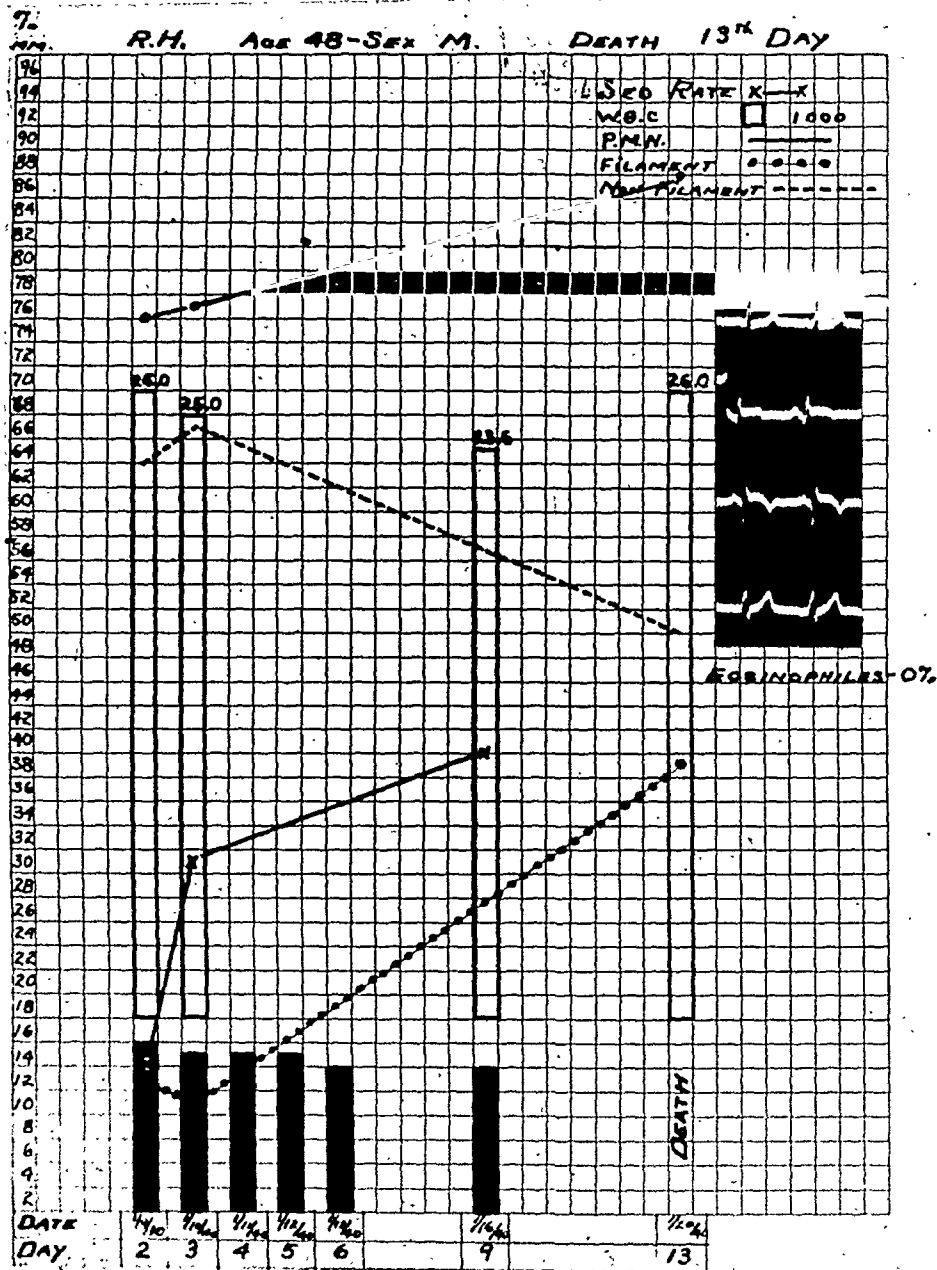


Chart V.—Showing only slight changes in the coagulation band, but high leucocyte count and rising sedimentation curve.

together with elevation of the leucocyte count, sedimentation rate, and nonfilament estimate, indicated myocardial infarction. His progress was satisfactory, and was accompanied by a gradual lengthening of the coagulation band and a decrease in the sedimentation rate and leucocyte and nonfilament counts. Eosinophiles appeared in the smear September 13, and reached 2 per cent.

CASE 7.—(Chart VII) T. K., a white man, aged 48 years, with a long history of gastrointestinal complaints and arterial hypertension, had had normal electrocardiograms since 1937. Symptoms of angina pectoris began in 1938. He was admitted to the hospital March 7, 1940, because of substernal distress which had

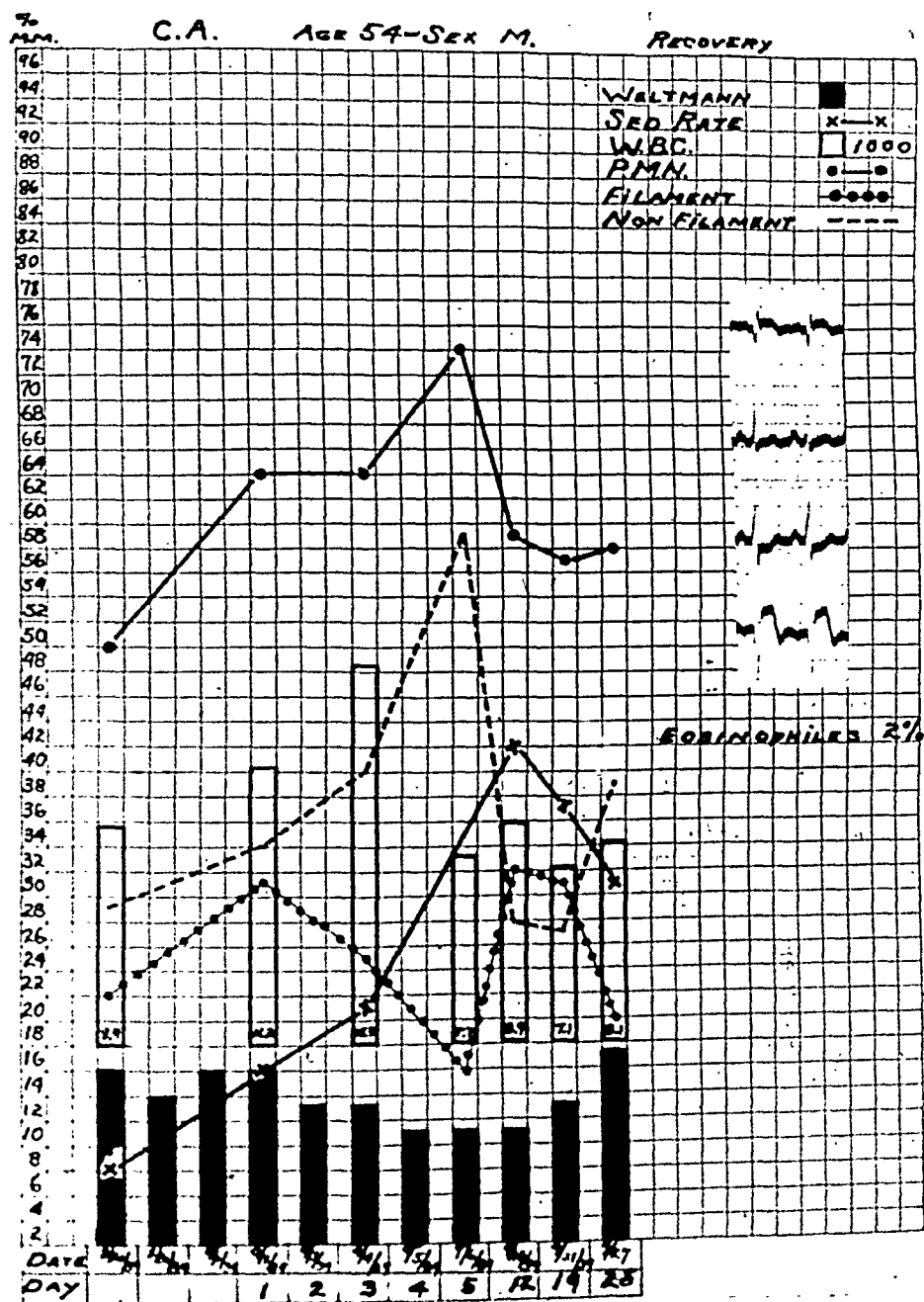


Chart VI.—Typical anterior infarction. Patient was admitted with severe coronary insufficiency, but did not show any changes in the electrocardiogram or coagulation band during first four hospital days. Infarction occurred on the fourth hospital day, and then typical changes, as shown, occurred.

been present since the previous evening, and had been partially relieved by nitroglycerine and codeine. Seven hours before admission the distress recurred, and morphine was required for relief. Electrocardiograms indicated myocardial infarction. The Weltmann coagulation band became shortened to $4\frac{1}{2}$ on the third day and returned to normal by the thirteenth day. The sedimentation rate was elevated, but gradually fell. The eosinophiles reached 2 per cent. His hospital course was uneventful, and he was discharged on the twenty-fifth day of his illness.

CASE 8.—(Chart VIII) Seven days before admission this 48-year-old white man (G. S.) experienced gripping substernal pain which radiated through to the back and persisted for seven hours. He remained at home in bed, and was asymptomatic

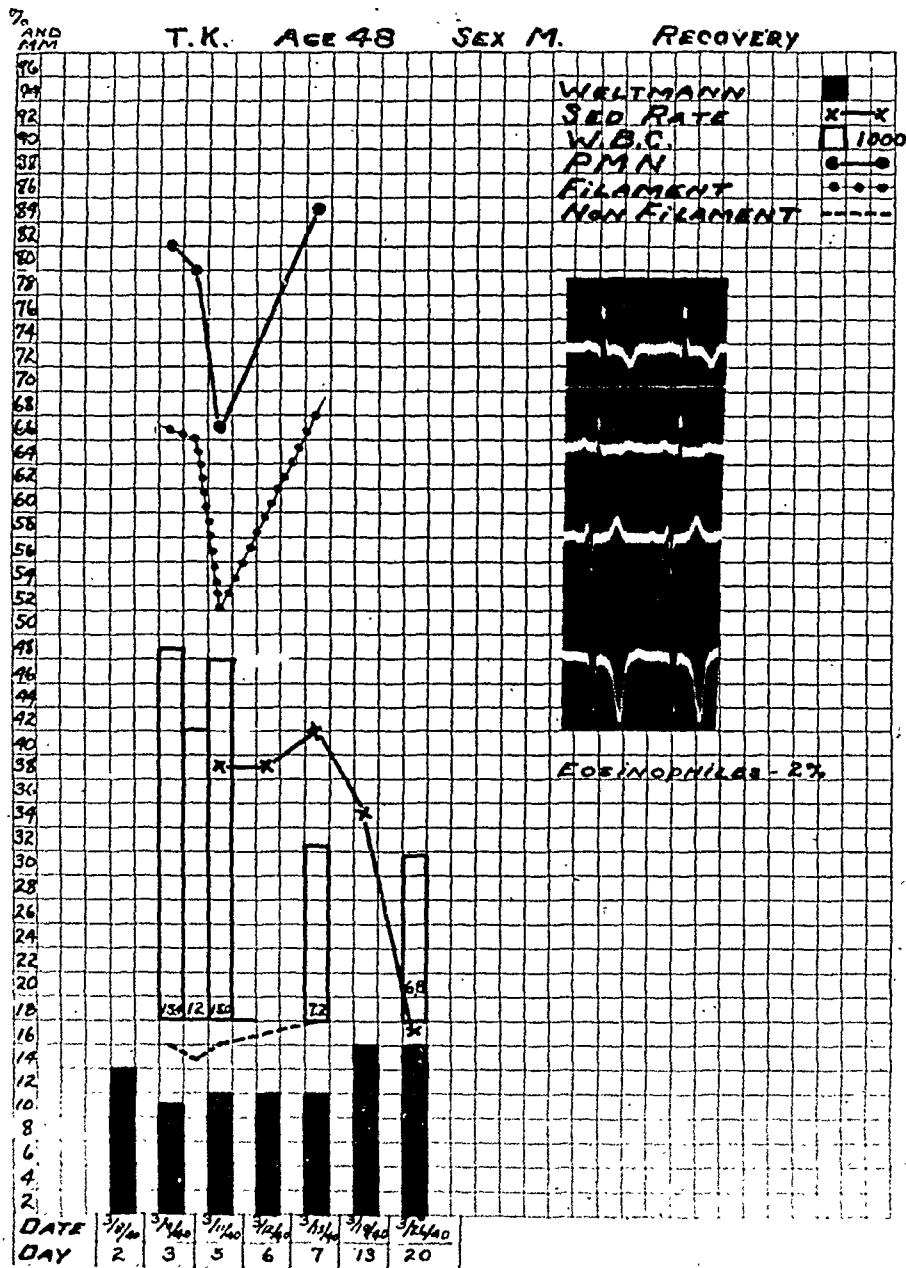


Chart VII.—Showing shortened coagulation band and high sedimentation rate and leucocyte count.

for two days. On the third day the pain recurred intermittently. On the day of admission the patient collapsed while en route to the bathroom. Electrocardiographic changes indicated anterior coronary artery occlusion. The Weltmann coagulation band became shortened to 4 on the sixth day, and then lengthened. The sedimentation rate and leucocyte count were elevated. Eosinophiles appeared on the tenth day and gradually rose to 9 per cent on the fourteenth day. His hospital course was uneventful except for a transient, presystolic gallop rhythm. The patient was discharged on the fifty-sixth day of his illness.

CASE 9.—(Chart IX) C. N., a white man, aged 48 years, was admitted to the hospital eighteen hours after the onset of a pressure sensation in the chest and

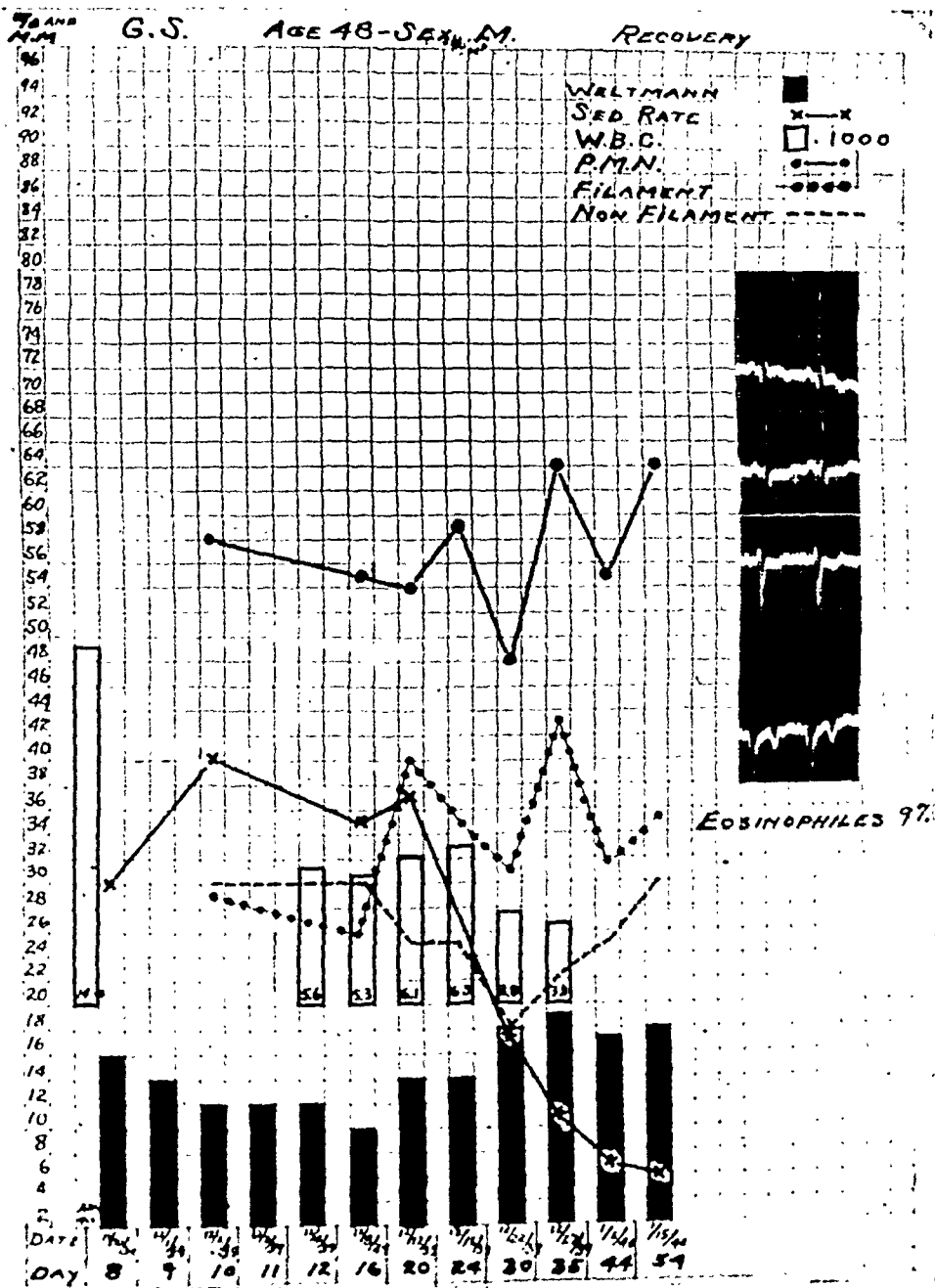


Chart VIII.—Showing typically high leucocyte count, elevated sedimentation rate, and shortened coagulation band. These returned to normal as healing occurred. Note high eosinophile count.

tightness in the throat. Twelve hours later these symptoms recurred. Serial electrocardiograms showed evidence of posterior coronary artery occlusion and transient auricular fibrillation. Weltmann coagulation bands of 4 and 2 were observed on the third and fifth days, respectively. Sedimentation rates, leucocyte counts, and nonfilament estimations were increased. All these slowly returned to normal. The lengthening of the coagulation band more closely paralleled the uneventful recovery of the patient. Eosinophiles appeared on the fifth day, but reached only 1 per cent. He was discharged on the twentieth day of his illness.

CASE 10.—(Chart X) Three days before admission to the hospital this 53-year-old white man (H. W.) experienced a severe, crushing pain in the left side of the

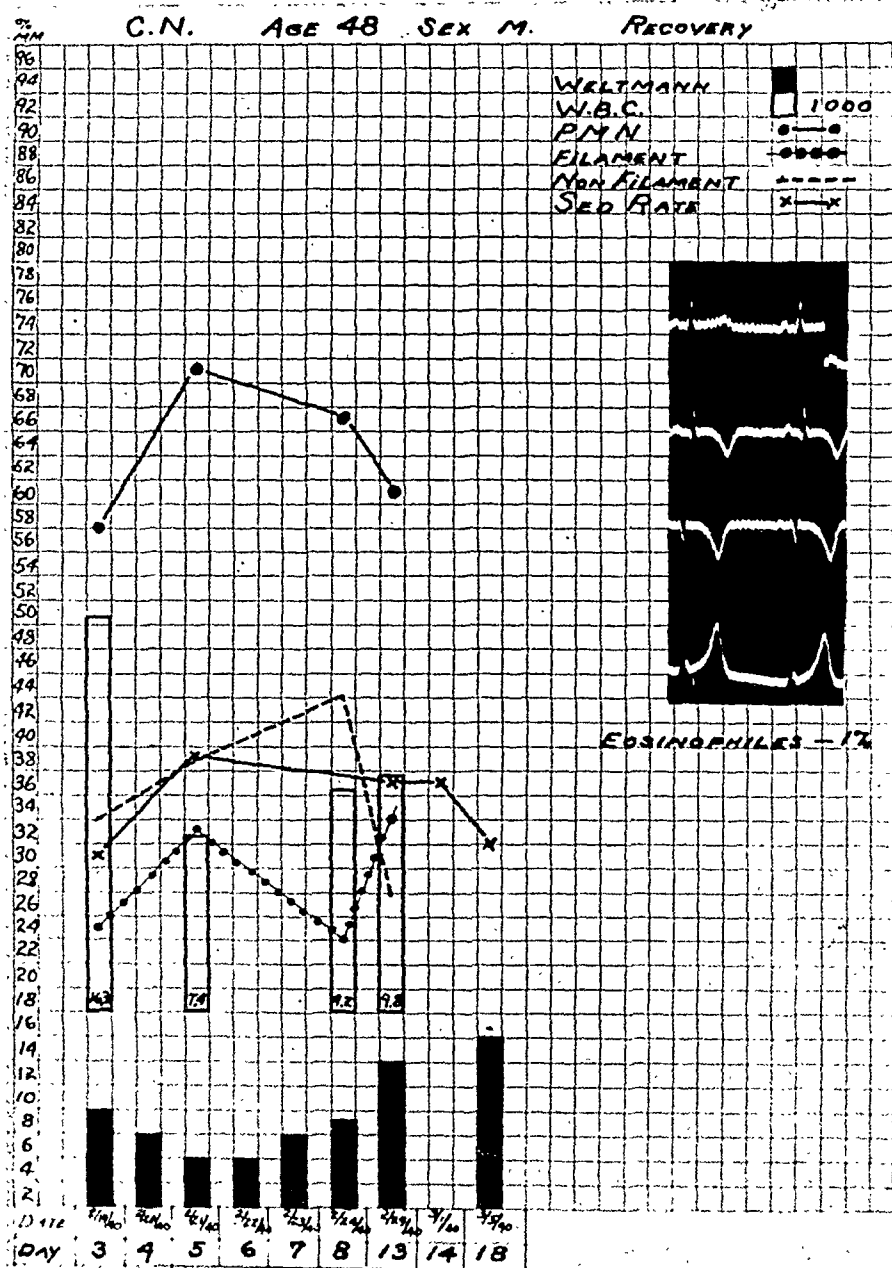


Chart IX.—Marked "shift to the left" in another case of severe myocardial infarction which returned to normal before sedimentation rate indicated healing.

CASE 11.—(Chart XI) H. W., a white man, aged 50 years, was admitted to the hospital August 25, 1939, complaining of severe substernal pain of three hours' duration which required morphine for relief. Cholecystectomy had been done in April, 1939, because of chronic cholecystitis and cholelithiasis. Although he was in a critical condition, his recovery was uneventful except for the occurrence of ventricular extrasystoles which were controlled by quinidine sulphate. He was discharged on the thirtieth day of his illness. The coagulation band fell from an initial level of 8 to 3 on the fifth day, then gradually lengthened as the patient's condition improved.

CASE 12.—(Chart XII) Three weeks before admission to the hospital this 62-year-old white man (J. Mc.) began to have angina pectoris. Three days before

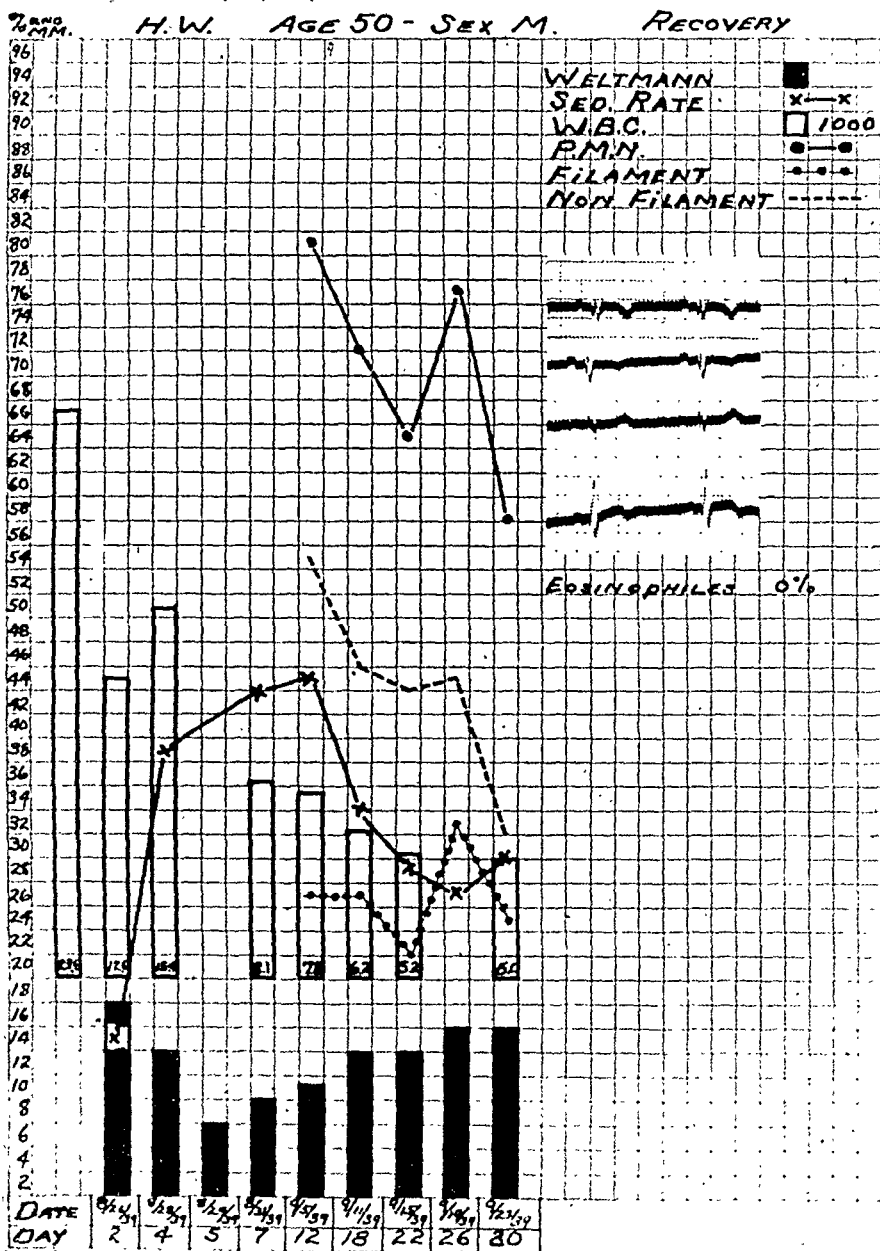


Chart XI.—Patient with extremely high leucocyte count and fairly marked shortening of the coagulation band, with return to normal after healing occurred.

admission the first of several prolonged attacks of substernal pain occurred; each lasted three to four hours. Clinical and electrocardiographic evidence indicated coronary artery occlusion. He was symptom free in the hospital until the seventh day of his illness, when he again experienced substernal pain, and his condition became grave. The electrocardiogram showed evidence of fresh infarction. On the twentieth day another, but milder, attack occurred. Thereafter his course was uneventful, and he was discharged on the forty-fourth day of his illness.

Note the rising Weltmann coagulation band and falling sedimentation rate on the fourth and seventh days. This would be expected with recovery from previous infarctions. The blood specimens were obtained before the infarction which oc-

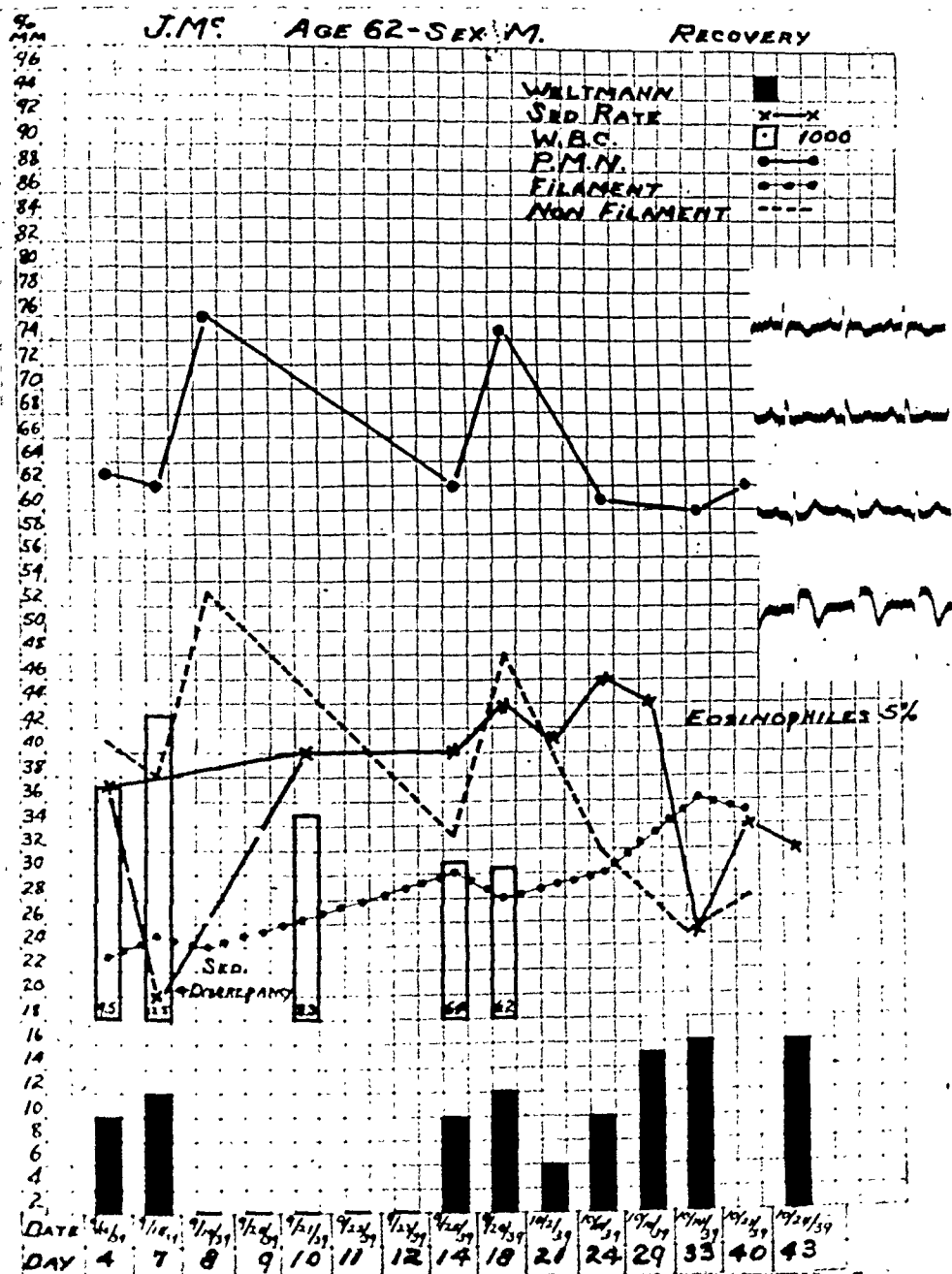


Chart XII.—Patient who showed complete absence of coagulation for ten days. Also note second occurrence of shortening after another infarction occurred on the twentieth day.

curred on the seventh day. After this attack, the coagulation bands remained markedly shortened while his condition was so critical. Here, too, the sedimentation rate, leucocyte count, and nonfilament estimates were increased. Eosinophiles appeared in the smear on Sept. 25, eight days after his first episode while in the hospital, and gradually rose to 5 per cent.

TABLE I
SHOWING THE COAGULATION BANDS AS RUN PROGRESSIVELY IN TWENTY-FOUR CASES

CASE	COAGULATION BANDS												
1	8	6	5	5	5	4	4	4	5	5½	6½	8	
	8	7	7	6	(Death on second admission)								
2	6½	3	3	3	1½	2½	(Death)						
3	4	3	2	1½	2½								
4	6	4											
5	7	6½	6½	6½	5	5	(Death)						
6	7	6	7	7	6½	6½	4½	4½	4½	5½	8		
7	6	4½	5	5	5	4	6	6	8	8½	7½	8	
8	6	4½	5	5	5	7	7						
9	4	3	2	2	3	3½	6	7					
10	7	6	5½	5	4½	7	8	8	8	8			
11	8	6	3	4	4½	6	6	7	7				
12	4	5	0	0	0	0	0	4	5	2	4	7	8
13	8	6	2	2½	6	8	(Died 1 month later of second infarction)						
14	0	1½	2½	(Death)									
15	7½	7	6	7	7	8							
16	5	3½	4½										
17	5½	1½	0	2½	2								
18	6	5	5	5	5	5	5	5					
19	8	7	7	6	6	6	5½						
20	8	8	7	8	8	6							
21	8	8	7	7	4½								
22	8	7	7	6	6	6	7						
23	8	8	8	7	6	6	6	7					
24	7	6½	6	6	6								

Table I is a summary of the coagulation bands in the entire series of twenty-four cases. Twelve of these have been presented in detail. In the remaining cases the coagulation bands, clinical course, and outcome of the disease correspond to the observations in the twelve cases recorded.

DISCUSSION

The Weltmann serocoagulation reaction has been used as a nonspecific indicator of activity in a number of conditions. Many investigators have found empirically that the coagulation band is shortened ("shift to the left") in infections and other processes characterized by tissue destruction. When fibrosis has occurred the band of coagulation is lengthened ("shift to the right"). Since myocardial necrosis, followed by healing by fibrosis, is the sequence of events in coronary artery occlusion, it seemed likely that this nonspecific test would be a valuable aid in diagnosing and in following the progress of the condition.

In this study we have compared the leucocyte counts, nonfilament estimates, sedimentation rates, eosinophile counts, and Weltmann reactions in twenty-five cases of coronary artery occlusion. Twelve illustrative cases have been reported. During the early, acute stages of

the infarction, beginning on the second or the third day, the coagulation band became progressively shortened, and reached its minimum by the fifth to the seventh day. This "shift to the left" affords some index of the extent of myocardial necrosis. An abrupt, extreme (to tube 1 or 2), or persistent left shift would indicate either a large infarction or slow healing, and therefore a more serious prognosis. Conversely, a coagulation band which is only moderately shortened or promptly returns to normal has been found to be associated with satisfactory healing and a good prognosis. As repair proceeds by fibrosis, the coagulation band lengthens again to normal. Large areas of fibrosis, old or recent, result in a shift to the right, beyond normal, to tube 8 or 9 (as in Cases 8 and 10). The Weltmann reaction, then, is a manifestation of the actual pathologic course of the disease.

In the presence of coronary artery insufficiency which produces myocardial ischemia without actual infarction, the coagulation band is unchanged. The Weltmann test is useful in differentiating between these two conditions. This is well illustrated in Case 6. While still under observation in the hospital this patient had coronary artery occlusion, accompanied by a typical shift to the left.

We have compared the Weltmann reaction with the sedimentation rate throughout our series because the latter procedure has been so extensively used in following cases of coronary artery occlusion. The sedimentation rate is known to be increased by destructive changes in the body, as well as by repair, whereas the coagulation band is shortened by the former and lengthened by the latter. Certain physiologic conditions, such as normal pregnancy and the ingestion of food, alter the sedimentation rate. It may vary in the same patient at different times during the day. These variations are not observed with the Weltmann test, which more closely reflects the true nature of the pathologic changes and the clinical course of the patient.

Our observations on the eosinophile percentages in this group of patients are consistent with those of Goodrich and Smith.¹⁷ In the cases of fatal occlusion they found no eosinophiles up to the fifth day. The number increased slowly to 1.6 per cent on the tenth day, and then fell to zero on the twelfth day. In the recovered group, eosinophiles appeared earlier and rose to 3.6 per cent on the fifteenth day.

The close parallelism between the changes in the Weltmann coagulation band and the nonfilament count is also to be noted. Our observations confirm those of Goodrich and Smith¹⁷ that the average nonfilament count is higher in the cases of fatal occlusion than in patients who recover. The eosinophile and nonfilament counts are apparently related to the evolution of the myocardial infarction, and give valuable information in estimating the prognosis.

There are two complicating factors which must be considered in interpreting the coagulation band. The presence of fibrotic processes,

old or new, cardiac or extracardiac, may interfere with the "shift to the left" which is indicative of the true extent of the infarction. However, a careful past history and clinical study of each patient will clarify this point, as is illustrated in Cases 1 and 10. Myocardial insufficiency will also prevent as much shortening of the coagulation band as would otherwise be expected. This is illustrated in Cases 4 and 5. Careful examination of the patient should disclose this complication, and obviate any confusion in interpreting the Weltmann reaction under these circumstances.

We believe that the Weltmann serocoagulation reaction reflects the true evolution of myocardial infarction more accurately than any of the many other nonspecific tests now available. It is of distinct value in diagnosis and prognosis. By frequent charting of the coagulation band, together with the results of the other nonspecific laboratory tests, one obtains diagnostic and prognostic information which is superior to that gained from any one procedure alone.

SUMMARY

The serocoagulation test of Weltmann has been compared with other diagnostic and prognostic blood studies in coronary occlusion with myocardial infarction.

It compares favorably with these procedures.

With large infarctions a marked "shift to the left" in the coagulation band occurs, so that it is an index of degree of infarction.

Healing of the infarction can be followed by the progressive change in the coagulation band.

In certain conditions the sedimentation rate may be altered by other, coexisting causes. The Weltmann test is not altered in such a manner, and reflects either the healing phase or early exudative or destructive phase.

It can serve both as a diagnostic and prognostic laboratory aid to the clinician.

We wish to express our appreciation to Dr. F. Janney Smith, Physician-in-Charge, Cardio-Respiratory Division, Henry Ford Hospital, Detroit, Michigan, for his permission to study these cases and for his valuable aid in the preparation of this paper.

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THE DIAGNOSTIC VALUE OF THE ELECTROCARDIOGRAM BASED ON AN ANALYSIS OF 149 AUTOPSY CASES

L. N. KATZ, M.D., A. M. GOLDMAN, M.D., R. LANGENDORF, M.D.,
L. G. KAPLAN, M.D., AND S. T. KILLIAN, M.D.
CHICAGO, ILL.

DURING the course of the last two decades we have evolved a procedure of interpreting electrocardiograms which is based on our own experiences and those of others. We felt that the accuracy of our diagnosis of normality and abnormality in the electrocardiogram, as well as the specificity of the various patterns that we have come to recognize, should be subjected to critical analysis. Such an analysis can best be made, we believe, by comparing electrocardiographic diagnoses, judged independently, with post-mortem observations in a random series of autopsy cases. This should reveal the merits of the diagnostic criteria we have utilized, and thus demonstrate the accuracy and worth of these criteria. The following report deals with the results of such a study.

MATERIAL AND PROCEDURES USED

All the autopsy cases in the files of the department of pathology from January, 1937, to May, 1940, were examined, and those in which electrocardiograms had been made were selected for this study. A total of 149 consecutive autopsy cases, with electrocardiograms, were obtained. In many of these cases serial electrocardiograms were available; some extended over a period of nine years.

After the autopsy cases had been selected, the electrocardiograms were analyzed independently as to their normality and abnormality, and the abnormalities were judged as nonspecific or specific with respect to the various patterns which we now recognize. In no case were the anatomic or clinical data consulted, and only the age of the patient was known; this was to insure an objective analysis according to our electrocardiographic standards. When serial electrocardiograms were available, the case was included only when the last tracing was taken shortly before the death of the patient. However, electrocardiograms which showed a cardiac strain pattern and were recorded within two months of the patient's death were not discarded. In 86 cases there was only one tracing; in 14 cases no chest leads were available; in 56 cases lead CF_2 was the only chest lead; in the others both leads CF_2 and CF_4 were available. The limitations of single records and electrocardiograms without chest leads in differentiating patterns are obvious.

Once the electrocardiograms were classified, the interpretations were correlated with the anatomic reports, and it was decided whether or not the electrocardiogram and autopsy observations were in accord. In deciding whether cardiac hypertrophy was present, the patient's age, body weight, heart weight, and the thickness of the

From the Cardiovascular Department of Michael Reese Hospital, Chicago, Ill.
Aided by the A. D. Nast and Emil and Fanny Wedeles Funds for Cardiovascular Research.

Received for publication March 28, 1942.

walls of the two ventricles were considered. Otherwise, the gross and histologic observations were used in making the correlation. The average normal heart weight was taken as 25 grams at three months, 125 grams at 12 years, and 200 grams at 17 years. In adults, weights of 300 and 250 grams, respectively, were considered the average normals for males and females. The average thickness of the ventricular wall was taken as 1.0 cm. for the left and 0.3 cm. for the right.¹ At times there was a discrepancy between the thickness of the ventricular wall and the heart weight. In such cases, more attention was placed on the weight of the heart than on individual measurements of thickness, for cardiac dilatation can decrease the latter. In borderline cases of heart weight, the decision was made by correlation with body weight.

The records were first divided into normal and abnormal electrocardiograms to see whether or not the anatomic changes were in accord; after this the various patterns we now recognize were catalogued separately and correlated as to discrepancy with the anatomic observations. All discrepancies were separated and analyzed in detail. The following patterns were separated from each other:

1. Normal record.
2. Nonspecific abnormal record.
3. Left ventricular preponderance without myocardial infarction.
4. Right ventricular preponderance without myocardial infarction.
5. Combined left and right ventricular strain without myocardial infarction.
6. Congenital heart disease.
7. Recent myocardial infarction.
8. Old, healed myocardial infarction.
9. Recent diffuse pericarditis without recent myocardial infarction.
10. Recent diffuse pericarditis with recent myocardial infarction.
11. Acute cor pulmonale.
12. Chronic cor pulmonale.
13. Mitral P wave.
14. Cor pulmonale P wave.

In our series there were no specific electrocardiographic patterns of acute diffuse glomerulonephritis, myxedema heart, hyperthyroid heart, beriberi heart, or chronic coronary insufficiency.² No separate classification of cases of prolonged electrical systole was made; this abnormality, like all others which did not fit into any of the specific patterns, was put under the heading of nonspecific abnormalities. The formula $QRST = 0.39 \sqrt{C} \pm 0.04$ (where C equals cycle length) was used³ to ascertain which electrical systoles fell within the normal range.

In several instances, records which showed more than one pattern were found as follows: Six were classed as right ventricular preponderance and mitral P wave, two were classed as recent myocardial infarction and recent diffuse pericarditis with recent myocardial infarction, two as chronic cor pulmonale and cor pulmonale P wave, one as mitral P wave and recent myocardial infarction, two as mitral P wave and nonspecific abnormalities, one as mitral P wave and left ventricular preponderance, one as mitral P wave and combined left and right ventricular strain, one as congenital heart disease and right ventricular preponderance, one as cor pulmonale P wave and combined left and right ventricular strain, and one as recent myocardial infarction and cor pulmonale P wave. Two were listed under three headings: One as combined left and right ventricular strain, chronic cor pulmonale, and cor pulmonale P wave; and the other as recent diffuse pericarditis without recent myocardial infarction, right ventricular preponderance, and mitral P wave. This made a total of 170 classifications for the 149 cases.

The final step was to classify the autopsy observations into separate categories and check the electrocardiographic patterns for each.

THE CRITERIA USED FOR THE VARIOUS PATTERNS

Since the value of an analysis such as ours depends on the criteria used in classifying the records, it is worth while to describe them briefly. The details of most of these patterns are considered elsewhere.^{4*}

(a) *Records were regarded as normal* when the rhythm was of sinus origin without tachycardia (rate under 100) and without more than an occasional premature systole; when the P-R interval was between 0.12 and 0.21 second; when the QRS complex was 0.10 sec. or less in duration, did not show marked slurring or notching, and had an over-all dimension of more than 15 mm. (1.5 millivolts) in the limb leads; when the QRS pattern indicated absence of axis deviation or evidence only of right or left axis shift without evidence of ventricular preponderance (discussed below); when a Q wave (defined as an initial inverted phase of a diphasic QRS measuring $\frac{1}{4}$ or more of the upright phase) was absent; when QRS was more than 8 mm. tall in leads CF_2 and CF_4 ; when QRS in lead CF_2 had only two phases of the $|/|$ type which were not less than 3 and 5 mm., respectively, in size; when QRS in lead CF_4 had only two phases of the $|/|$ type and the upright phase was not less than 3 mm., or when it had only one phase of the \wedge type, or when it had two phases of the $|/|$ type or three phases of the W type with an initial inverted phase not more than 3 mm. in depth; when S-T depressions of not more than $\frac{1}{2}$ mm. and S-T elevations of not more than 2 mm. were present in any of the limb leads; when S-T was isoelectric or elevated less than 2 mm. in leads CF_2 and CF_4 ; when T in Leads I and II was upright and not notched (provided it did not have the upright coronary T pattern); when T in leads CF_2 and CF_4 was upright and not taller than 8 and 10 mm., respectively. However, in analyzing the S-T and T deflections, the combined S-T-T complex was considered as a unit, and, when there was slight S-T deviation, the contour of the S-T-T was considered of more significance than the degree of the S-T deviation.

(b) *Records were regarded as showing nonspecific abnormalities* when they did not fit the foregoing description of normal and did not fall into any of the specific patterns. Certain arrhythmias, like heart block of various types, auricular fibrillation, frequent premature systoles, paroxysmal ventricular tachycardia, and nodal rhythm would also be placed in this group, even if the contour were normal. However, none of these arrhythmias occurred in this series in conjunction with a normal contour of the electrocardiogram.

(c) *Patterns of heart strain.* These were divided into three categories, namely, left ventricular preponderance, right ventricular preponderance, and combined left-and-right-sided strain. Axis deviation attributable to the normal variant, axis shift, was excluded by the electrocardiographic appearance. Axis deviation associated with recent myocardial infarction or recent massive pulmonary embolism was also excluded because the axis deviation could have been attributed to the latter circumstances and not to cardiac hypertrophy. Similarly, axis deviation with a QRS duration of 0.12 sec. or more was not included, but was classed instead as a nonspecific abnormal curve showing intraventricular block.

The criteria for diagnosing *right ventricular preponderance* (lower part of Fig. 1) were a QRS duration of less than 0.12 sec.; absence of evidence of recent myocardial infarction or acute cor pulmonale; QRS in lead I mainly downward or equiphasic and of the S type (an S wave was defined as a second inverted phase of a diphasic QRS, measuring $\frac{1}{4}$ or more of the preceding upright phase); QRS_2 upright, equiphasic, or mainly downward, with an S wave in the latter two circumstances; and QRS_3 mainly upright. This is distinguished from normal right axis shift, in which QRS_1 is mainly upright and small, or diphasic with an S wave less than the upright phase. The differentiation between the two patterns will become clearer by comparing right axis

*Appropriate corrections were made for children.

†Inverted N.

shift (RAS) and right ventricular preponderance (RVP) in Fig. 1, in which typical patterns (including the S-T-T) are diagrammatically depicted.

The criteria for diagnosing *left ventricular preponderance* were those recently published from this department.⁵ They fall into four categories, namely, type 1,

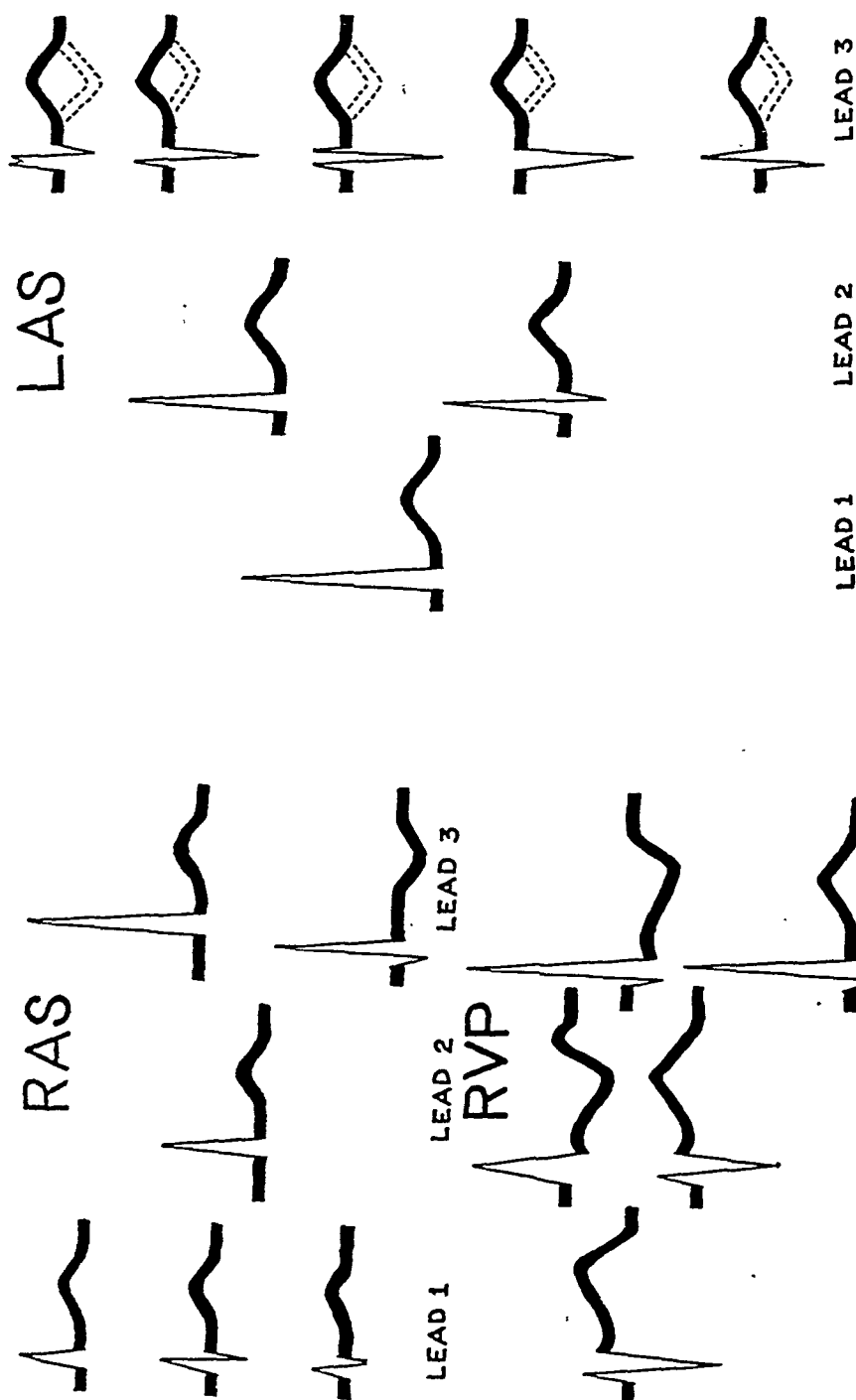


Fig. 1.—Diagrams of the typical appearance of the ventricular complex in the limb leads in right axis shift (RAS), upper part of figure, and in right ventricular preponderance (RVP), lower part of figure. In right ventricular preponderance, Leads II and III may also resemble the contours shown in right axis shift. Discussed in text.

type 2, mixed type, and concordant type. In all, QRS is less than 0.12 sec., and evidence of recent myocardial infarction and acute cor pulmonale is absent. In type 1 (Fig. 3) there is an upright, relatively tall QRS_1 , associated with an inverted QRS_2 , or mainly inverted QRS_2 of the S type, with a very small QRS_2 (2 or

3 mm.) or a mainly inverted or equiphasic one of the S type, and without S-T-T abnormalities. In type 2 (Fig. 4) there are a tall, upright QRS_1 and QRS_2 , a depressed $S-T_1$ (and $S-T_2$), a low, diphasic or inverted T_1 (and T_2), and an inverted QRS_3 . In the mixed type (Fig. 4) there is a combination of the QRS pattern of type 1 and

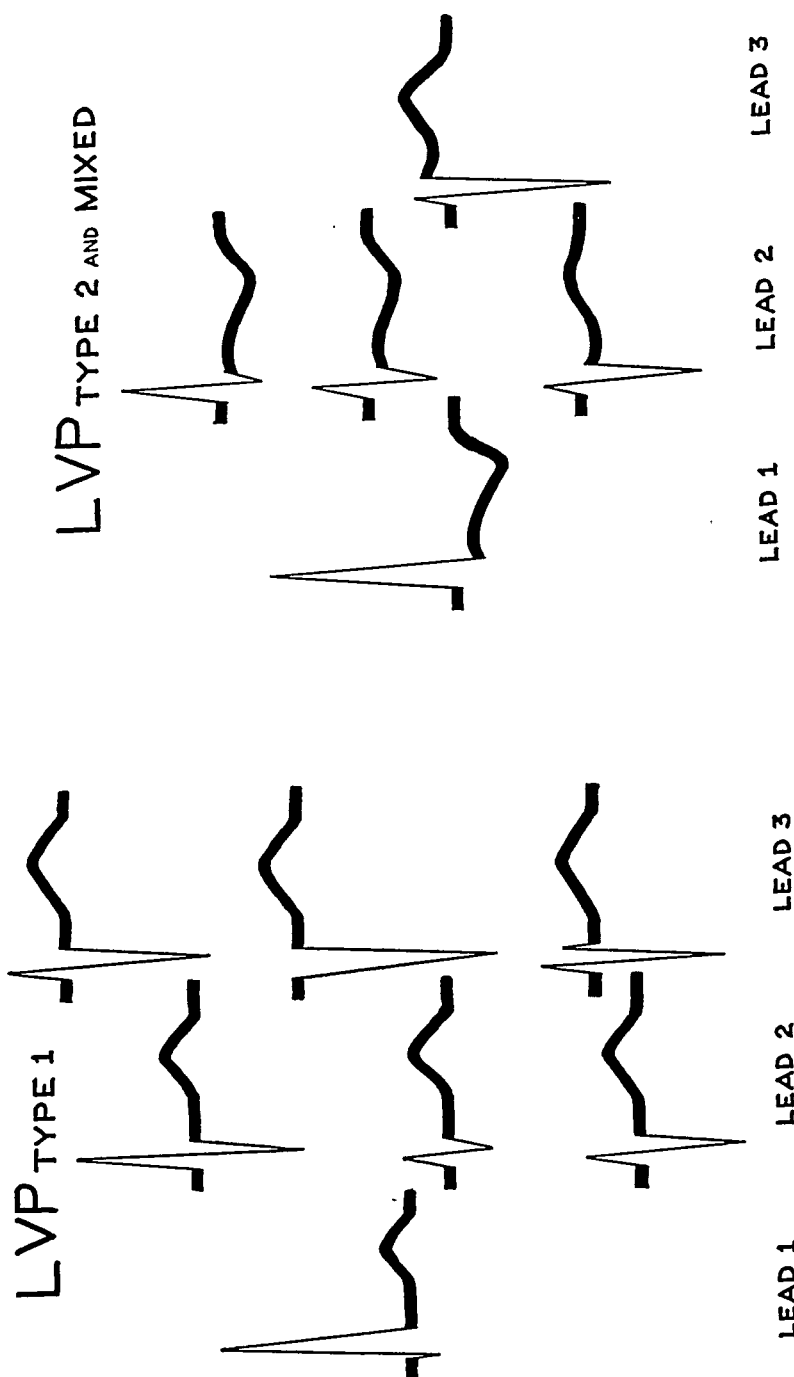


Fig. 4.—Diagrams of the typical appearance in the second and mixed types of left ventricular preponderance (LVP type 2 and mixed). The upper curve of Lead II is encountered in the second type of left ventricular preponderance; the other two occur in the mixed type. Discussed in text.

Fig. 3.—Diagrams of the typical appearance in the first type of left ventricular preponderance (LVP type 1). Discussed in text.

the S-T-T pattern of type 2. In the concordant type (Fig. 5), the S-T-T pattern is like that of type 2, but QRS is upright in all the limb leads. Left ventricular preponderance is distinguished from normal left axis shift, in which QRS_3 is small, diphasic with an S wave, or inverted, but Leads I and II are normal in appearance.

The differentiation between left ventricular preponderance and left axis shift will become clearer by comparing Fig. 2 with Figs. 3, 4, and 5, in which typical patterns (including the S-T-T) are diagrammatically depicted.

The criteria for diagnosing *combined left and right ventricular strains* were a QRS of less than 0.12 sec., absence of evidence of recent myocardial infarction and acute cor pulmonale, and the presence in the QRST complex of some features pointing to right, and others to left, ventricular preponderance. Two types of QRST would be placed in this group. In the first, QRS_1 is small and diphasic, QRS_2 is diphasic or mainly inverted, and QRS_3 is inverted, with S waves in Leads II and III (and Lead I). A second type consists of a QRS pattern indicating right ventricular strain and an S-T-T pattern pointing to left ventricular strain.

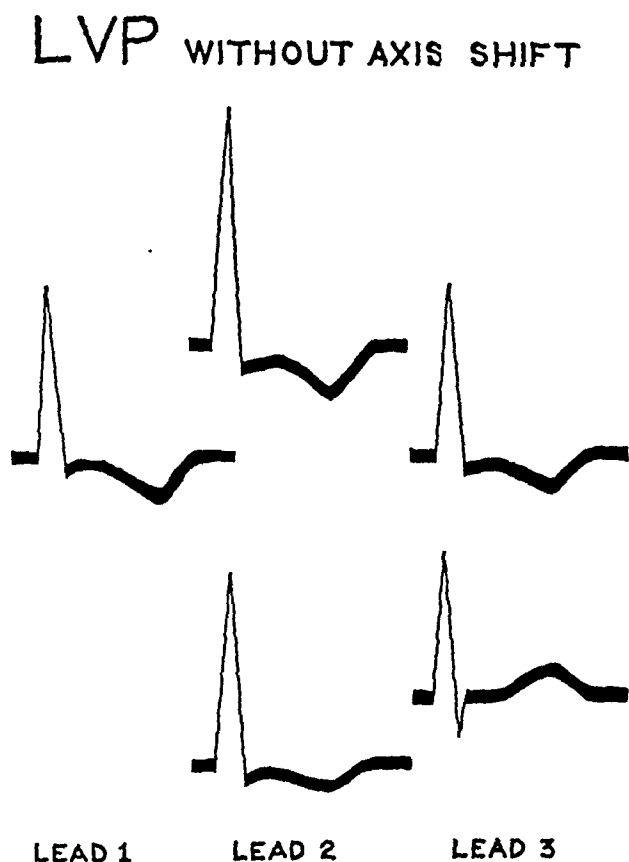


Fig. 5.—Diagrams of the typical appearance in the concordant type of left ventricular preponderance (LVP without axis shift). Discussed in text.

(d) *Congenital heart disease* was diagnosed when large, diphasic QRS complexes were present in two or all three of the limb leads.⁷

(e) The diagnosis of *recent myocardial infarction* was made when the generally recognized patterns of infarction were present in both limb and/or chest leads. The cases were listed as the anterior wall type, posterior wall type, combined anterior and posterior wall type, and atypical patterns. The details of diagnosis are discussed elsewhere at some length.⁴

(f) The diagnosis of *recent diffuse pericarditis with and without recent myocardial infarction* was made according to established criteria recently summarized elsewhere.⁸

(g) *Acute cor pulmonale* (massive pulmonary embolism) was diagnosed when the classical pattern of McGinn and White⁹ was present, or when the classical picture described elsewhere in a report from this department¹⁰ was found.

(h) *Chronic cor pulmonale* was diagnosed when, with right ventricular preponderance, *cor pulmonale* P waves (described below) were seen.

(i) The following two P-wave patterns were distinguished: The classical *mitral P wave*, indicative of chronic left auricular strain, in which P in Leads I and II were broad and notched and P₃ usually diphasic; and *cor pulmonale P wave*, presumably indicative of chronic right auricular strain, in which P₂ and P₃ were tall and peaked and P₁ was small.¹¹ These P-wave patterns were found to be associated with abnormalities of the QRS-T complex in this series.

DISCUSSION OF RESULTS

Attention should first be directed to the fact that this series is small; therefore, conclusions derived from it should be considered tentative pending similar analyses of much larger series. Nevertheless, even this small series permits several important deductions.

TABLE I

THE RELATION OF THE ELECTROCARDIOGRAM TO THE AUTOPSY OBSERVATIONS

ELECTROCARDIOGRAPHIC PATTERNS	AUTOPSY OBSERVATIONS	
	NORMAL HEARTS	ABNORMAL HEARTS
8 Normal	7	1
141 Abnormal	0	141
149 Total	7	142

The Accuracy of the Diagnosis of Normality and Abnormality.—Table I shows the correlation of our autopsy and electrocardiographic interpretations in the 149 cases of this series. It will be seen that there were 141 abnormal electrocardiograms, and that, in all of these cases, there was evidence of cardiac damage at necropsy; this is a surprising degree of consistency, in that no electrocardiogram was abnormal when the heart was normal. This is a much better correlation than in a previous report,¹² and may indicate either (a) that this was a coincidence which would not occur if we had analyzed a much larger series, (b) that our criteria of abnormality of the heart at necropsy were not as rigid as those of previous workers, or (c) that our criteria of electrocardiographic abnormality were better than those of previous authors. It should be pointed out that the diagnosis of heart disease at necropsy was arrived at by us independently of the electrocardiographic interpretation. Only eight electrocardiograms were interpreted as normal, and in seven of these cases the heart at autopsy was also normal. In the eighth case, however, in which the electrocardiogram was regarded as probably normal (cf. Fig. 6A and Table III), the heart showed some coronary sclerosis with myocardial fibrosis and left ventricular hypertrophy; this person was 82 years of age.

The general deduction from these observations is that the electrocardiogram is a surprisingly good index of normality or abnormality of

there were evidences of one or another form of ventricular hypertrophy curve. In six others there was an axis shift, and in one there was none. These seven exceptions included a normal record, 5 nonspecific abnormal records, and 1 which showed only the pattern of recent diffuse pericarditis without recent myocardial infarction (which was confirmed at necropsy). Further, the agreement of the electrocardiogram in cases of isolated left or isolated right ventricular hypertrophy, as found at necropsy, was surprisingly good, namely, 21 out of 24 and 7 out of 8, respectively. It is, nevertheless, important to point out that hearts may be relatively large without producing any of the hypertrophy

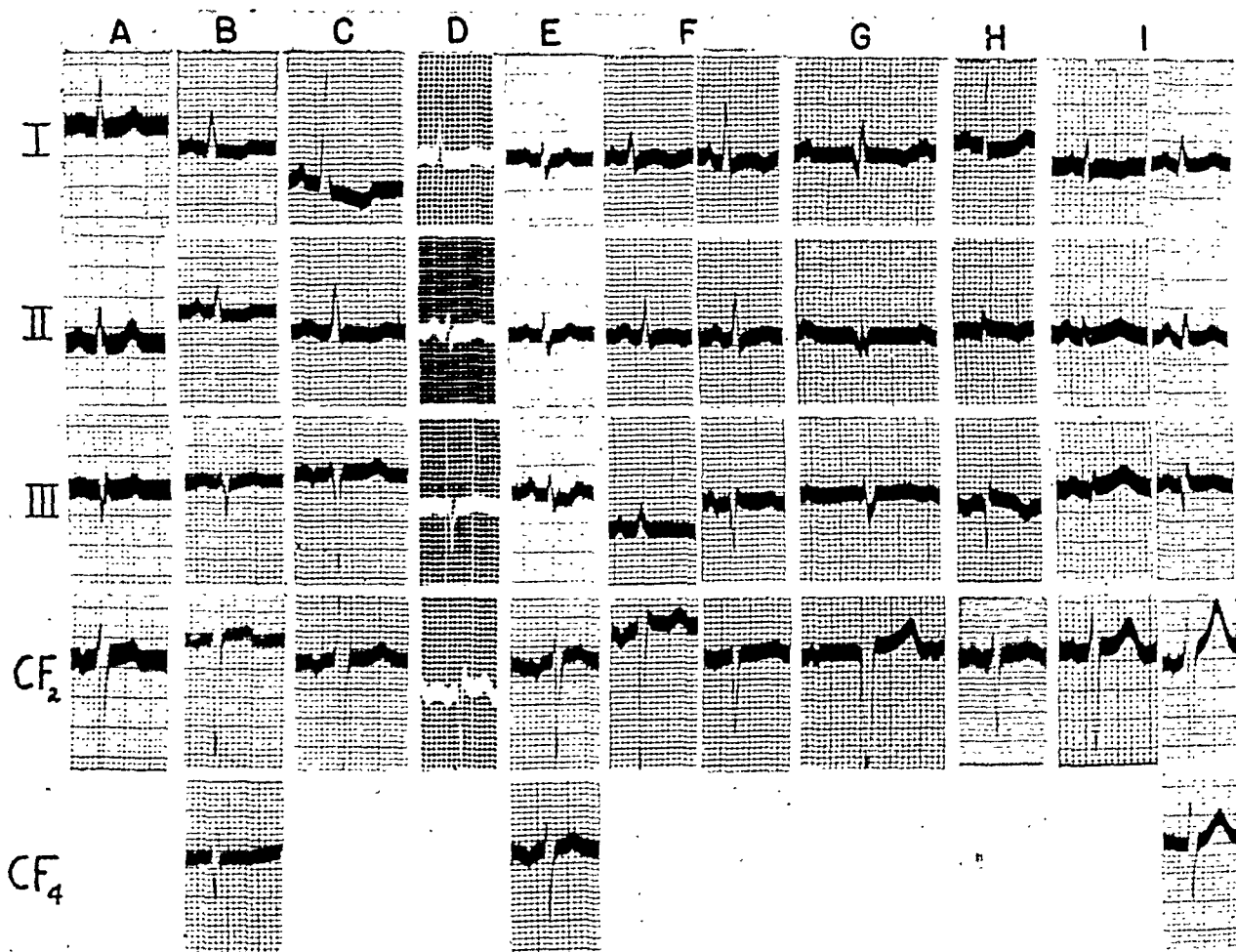


Fig. 6.—Portions of electrocardiograms in cases in which there were discrepancies between the electrocardiographic pattern and the anatomic changes. The details of each are summarized in Table III. Discussed in text. In *F* and *I*, two records from the case are shown; they were taken 3 days and 49 days apart, respectively.

patterns. Fig. 6Q is the record in a case in which the heart weighed 825 grams; there was hypertrophy of both ventricles but only left axis shift and nonspecific abnormalities in the electrocardiogram.

The results of this study indicate that cardiac hypertrophy may be revealed in the electrocardiogram by specific patterns. However, the patterns of left ventricular preponderance occasionally occur in the

absence of ventricular hypertrophy, and, contrariwise, ventricular hypertrophy occurs without the electrocardiographic patterns. Furthermore, on occasion, the dominant strain on the two ventricles is also not revealed by the electrocardiographic pattern, but in most instances the correlation is surprisingly good.

Congenital Heart Disease.—In all three cases of the classical type of congenital heart disease the diagnosis was confirmed at necropsy. However, 4 cases of congenital heart disease were found at necropsy in this series (Table IV); in the fourth case the electrocardiogram showed only right ventricular preponderance. The classical pattern, therefore,

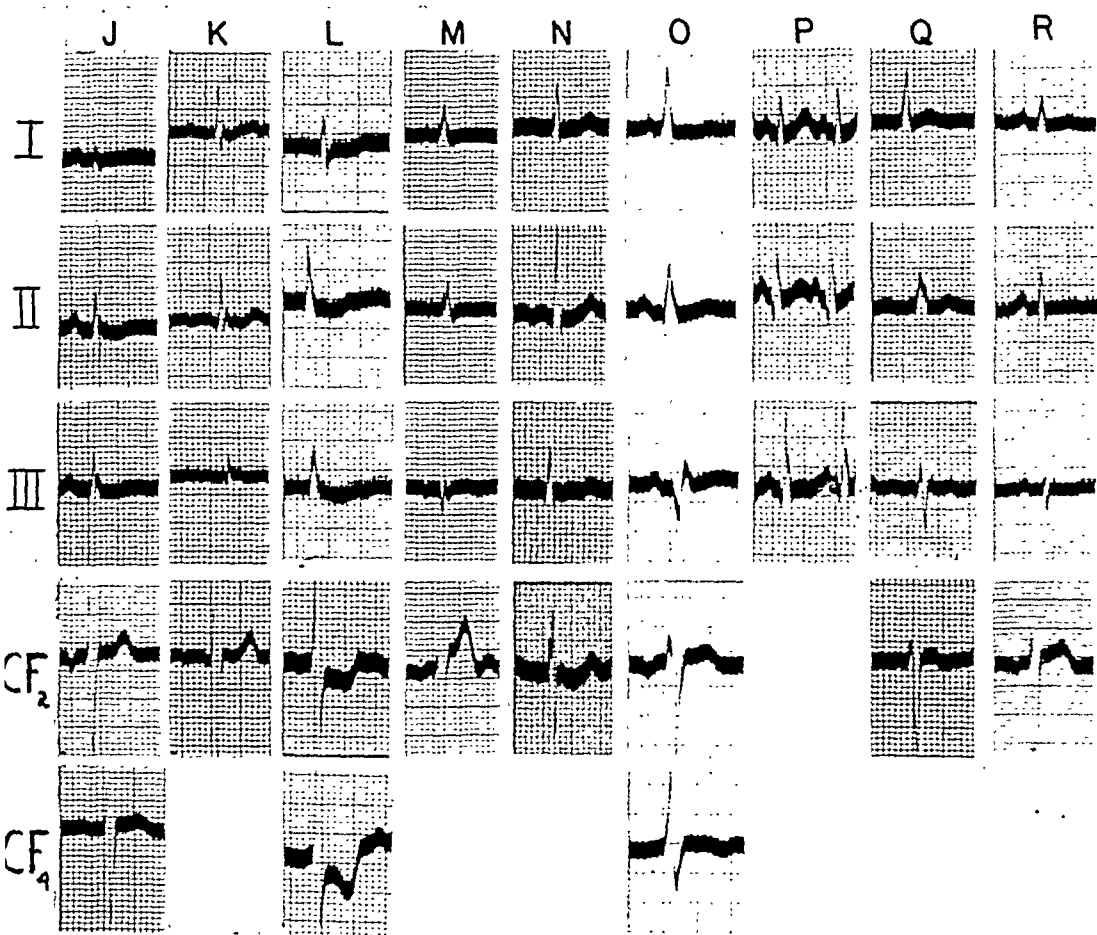


Fig. 6.

is diagnostic of congenital heart disease, but its absence does not rule out this condition. Schnitker¹⁴ found this pattern in 30 per cent of 106 cases of congenital heart disease proved at necropsy.

Myocardial Infarction.—In twenty-five cases in this series there were various patterns of recent myocardial infarction, and in one case there was a stabilized coronary pattern indicative of an old, healed myocardial infarct. In 22 of the cases with the pattern of recent infarc-

tion, the infarct was found at necropsy (Table II), and the age of the infarct agreed with the electrocardiographic evolution. In one, the case of old healed infarction, the infarct was found, but its location was inaccurately depicted (cf. Case 2 of anterior wall infarct type, Table III and Fig. 6*G*). In the other three cases, the electrocardiographic diagnosis of recent infarction was not substantiated at necropsy (Table III). In one case (cf. Case 1 of the anterior wall type, Table III and Fig. 6*F*), ventricular hypertrophy was found at necropsy and hypertension and terminal congestive heart failure were noted clinically; it would appear that terminal coronary insufficiency, accompanying the heart failure, gave rise to the coronary pattern and evolution.

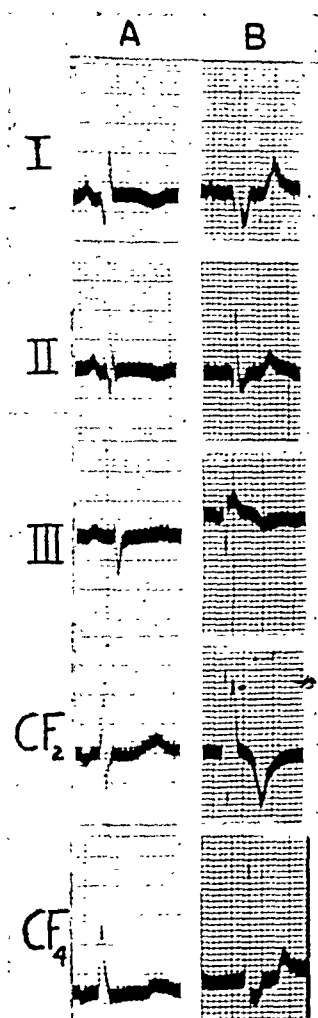


Fig. 7.—Portions of electrocardiograms in two cases in which the electrocardiographic pattern did not agree with the anatomic changes. *A* is a case of lateral wall infarction of the left ventricle in which the pattern described by Wood, Wolferth, and Bellet¹² did not occur. *B* is a case of massive pulmonary embolism in which there were nonspecific abnormalities in the form of intraventricular block of the second indeterminate (S) type. Discussed in text.

In the second case (cf. posterior wall type, Table III and Fig. 6*II*), the pattern was doubtless produced by the massive pulmonary embolism, superimposed on left ventricular preponderance, both of which were evident at necropsy. In the third case (cf. atypical pattern, Table

III and Fig. 6I), the suggestive pattern could have been caused by vitamin deficiency.

Thus there was surprising agreement as to the presence of infarction, its localization, and its age. This is in accord with a previous study.¹⁵ The fact that an old, healed infarct was not correctly located may indicate that other circumstances had resulted in chronic coronary insufficiency in the region indicated by the electrocardiogram, but this is obviously a speculation. Further, it has been our experience that in some patients, especially patients with coronary disease, the electrocardiogram may imitate the coronary pattern during heart failure. We have also recognized the possibility that massive pulmonary embolism may give a coronary pattern, and other conditions, such as beriberi heart, may show atypical coronary patterns on occasion.

In this series, 25 cases of recent myocardial infarction were found at necropsy (Table IV); in 22 of these the diagnosis was made by means of the electrocardiogram, as stated above, and in three others it was not. Thus, not only may recent myocardial infarction be diagnosed in the electrocardiogram when it is not present, but also, on occasion, its existence is not revealed in the electrocardiogram. Of the 3 cases in which it was overlooked, there was only left ventricular preponderance in 2 (cf. Cases 1 and 3 of second and mixed types, Table III and Fig. 6B and D), and, in the third, the abnormalities were nonspecific (cf. Case 4, Table III and Fig. 6M). Although, in this series, there was good agreement between the electrocardiographic and necropsy diagnoses, it is clear that (1) some coronary patterns of recent myocardial infarction are caused by other lesions, and (2) some recent myocardial infarctions are overlooked in the electrocardiogram. The electrocardiogram is, after all, only part of the armamentarium of the clinician, and reliance entirely upon it for even this condition is not justifiable either in the positive or the negative sense. Absence of the pattern does not exclude the lesion if the clinical manifestations are diagnostic. A positive pattern should be viewed in the light of the clinical picture in order to exclude the possibility of other diseases which can produce a similar pattern. When there is doubt, positive evidence should outweigh negative evidence.

Of the old, healed myocardial infarcts which were found at necropsy (Table IV), only one was diagnosed in the electrocardiogram and then was wrongly located (cf. Case 2, anterior wall infarct, Table III and Fig. 6G). In the other 6, either left ventricular preponderance (cf. Cases 1 and 2, of second and mixed types, Table III and Fig. 6B and C) or nonspecific abnormalities (cf. Cases 1, 2, 3, and 6, Table III and Fig. 6J, K, L, and O) were found, with nothing to suggest the infarction. This is in sharp contrast with myocardial infarction of recent origin. It is for this reason that we have made it a practice to separate recent from old infarction. Little is lost in this lack of ability to diagnose old infarction, for, unlike recent infarction, its presence does

TABLE III
SUMMARY OF CASES IN WHICH THERE WERE DISCREPANCIES

ECG. PATTERN (FIG. NO. WHERE ILLUSTRATED)	TOTAL NO. OF CASES	NO. OF DISCREPANCIES	INADEQUATE ECG. DATA	AGE	SEX	CHIEF CLINICAL FINDINGS	BODY WEIGHT KILOS	HEART WEIGHT GRAMS	LEFT VENT. THICKNESS, CM.	RIGHT VENT. THICKNESS, CM.	GROSS ANATOMY	MICROSCOPIC ANATOMY	NATURE OF DISCREPANCY
Within Normal Limits. (6A)	8	1	Single record	82	M	Diabetes mellitus	65	330	1.4	0.1	Coronary sclerosis; myocardial fibrosis; arteries rigid and in some areas almost occluded.	Fibers large and pale; increase in connective tissue.	For this age ECG is normal; however, there is a Q ₃ and a tendency to low voltage; no evidence of left ventricular preponderance.
Left Ventricular Preponderance Without Infarction.	33	3											
First Type.	6	0											
Second and Mixed Types.	26	3											
Case 1. (6B)				56	M	Congestive heart failure. B.P. 130/80	50	500	1.2	0.1 to 0.4	Marked coronary sclerosis; old and recent infarct of apical, lower septal, and lower ant. wall of left ventricle. Moderate pulmonary emphysema.	Marked necrobiotic changes in muscle fibers; marked increase in connective tissue.	ECG shows no evidence of old infarct; recent one occurred after ECG taken. However, diagnosis of left ventricular preponderance fits.

TABLE III—CONT'D

ECG. PATTERN (FIG. NO. WHERE ILLUSTRATED)	TOTAL NO. OF CASES	NO. OF DISCREPANCIES	INADEQUATE ECG. DATA	AGE	SEX	CHIEF CLINICAL FINDINGS	BODY WEIGHT KILOGRAMS	HEART WEIGHT GRAMS	LEFT VENT. THICKNESS, CM.	RIGHT VENT. THICKNESS, CM.	GROSS ANATOMY	MICROSCOPIC ANATOMY	NATURE OF DISCREPANCY
Case 2. (6K)			Single record, only CF _r	57	F	Congestive heart failure. B.P. 158/100	55	350	1.5	0.5	Old posterior infarct; marked coronary sclerosis; healed endocarditis of mitral and tricuspid valves.	Patchy fibrosis; enlarged myofibrils.	ECG shows no evidence of old infarct present at autopsy.
Case 3. (6L)			Single record	59	M	Rheumatic fever, abdominal pain.	60	350	1.0	0.3 to 0.5	Old posterior wall infarct. Mitral stenosis. Moderate coronary sclerosis. Multiple liver abscesses.	Increase fibrous tissue in post. wall. Myofibrils of right vent. swollen.	Digitalis contour in ECG, no evidence of old posterior wall infarct.
Case 4. (6M)			Single record, only CF _r	65	M	Sudden collapse. Congestive heart failure.	64	350	1.2	0.3	Recent post. wall infarct; marked coronary sclerosis. Pneumonia.	Neurotic fibers —posterior wall. Diffuse fibrosis.	Record taken at time of attack; this may explain failure of ECG to show infarct. Patient died before repeat record could be taken.
Case 5. (6N)			Only CF _r	32	M	Rheumatic heart disease. Conges. heart failure.	70	500	1.4	0.3	Healed endocarditis mitral and aortic valves with insufficiency and stenosis. Patent coronary arteries.	Diffuse increase in connective tissue. Enlarged myofibrils.	Depression of S-T, ascribed to digitalis. No evidence of left or right ventricular strain.

Case 6. (60)				73	M	Angina pector- is; pleural effusion.	N.G.	325	1.2	0.3	Carcinoma of lung ex- tending into left auricular wall; old anterior wall in- farct.	Dense connec- tive tissue in region of in- farct. Tumor cells in left auricle.	ECG fails to show evidence of old an- terior wall infarct. If anything Q_a would point to pos- terior wall infarc- tion; invasion of heart by tumor may account for changes.
Case 7. (6P)			Single record, no CF.	5	M	Abdominal pain; bloody stools; albu- minuria; B.P. 190/140	20	125	--	--	Acute peritonitis and enteritis. Hypopla- sia of right kid- ney. Hypertrophy of left ventricle.	No microscopic observation.	No ECG evidence of left ventricular pre- ponderance found at autopsy.
Case 8. (6Q)			Single record, only CF.	52	F	Uremia. Con- gestive heart failure. B.P. 228/112	N.G.	825	2.1	0.5	Plaques in coronary arteries. Marked hypertrophy of heart. Nephro- sclerosis.	Diffuse increase in connective tissue.	ECG shows only left axis shift and noth- ing to indicate hy- pertrophy found at autopsy.
Case 9. (6R)			Single record, only CF.	42	M	Rheumatic heart disease. Congestive heart failure.	N.G.	500	1.7	0.3	Acute vegetative en- docarditis; old mi- tral and aortic en- docard.	Swollen granu- lar fibrils; scattered leu- cocytes and lymphocytes.	Left axis shift with low voltage. No evidence of hyper- trophy in ECG.
Total	170 patterns in 149 cases with 18 exceptions												

N.G. = Not given.

TABLE IV
THE ELECTROCARDIOGRAPHIC PATTERNS WITH DIFFERENT TYPES OF NECROPSY CHANGES

AUTOPSY OBSERVATIONS	NUMBER OF CASES	ELECTROCARDIOGRAPHIC PATTERN	
		AGREE	DISAGREE (FIG. NO. SHOWING ILLUSTRATION)
Hypertrophy of Left Ventricle	24 16 other cases not included because of: myocardial infarction—11; massive pulmonary embolism—2; intraventricular block in ECG—3.	21	3 1st showed right axis shift and non-specific abnormality (6P). 2nd showed left axis shift and non-specific abnormality (6E). 3rd was within normal limits (6A).
Hypertrophy of Right Ventricle	8 4 other cases not included because of: myocardial infarction—2; intraventricular block in ECG—2.	7	1 It showed combined right and left ventricular strain (6E).
Hypertrophy of Both Left and Right Ventricles	19 12 other cases not included because of: myocardial infarction—8; massive pulmonary embolism—1; intraventricular block in ECG—3.	15	4 1st showed left axis shift and diffuse pericarditis. 2nd showed left axis shift and non-specific abnormality (6Q). 3rd showed no axis shift and non-specific abnormality (6N). 4th showed left axis shift and non-specific abnormality (6E).
Congenital Heart Disease	4	3	1 It showed only right ventricular preponderance.
Recent Myocardial Infarction	25	22	3 2 showed only left ventricular preponderance (6B & D). 1 showed only nonspecific abnormality (6M).

Old Healed Myocardial Infarction	7	1 (6G)	6 2 showed only left ventricular preponderance (6B & C). 4 showed only nonspecific abnormality (6J, K, L & O).
Recent Diffuse Pericarditis Without Recent Myocardial Infarction	3	3	0
Recent Diffuse Pericarditis With Recent Myocardial Infarction	4	2 (seen in the S-T stage)	2 (seen in T stage) Gave no evidence of complicating pericarditis.
Acute Cor Pulmonale (Massive Pulmonary Embolism)	3	1	2 1st showed a posterior wall infarct pattern (6H). 2nd showed only intraventricular block of the 2nd indeterminate type (7B).
Chronic Cor Pulmonale	8	4 3 showed cor pulmonale P wave. 1 showed auricular fibrillation.	4 They showed no cor pulmonale P wave or auricular fibrillation.
Hypertrophy and (or) Dilation of Left Auricle	10 8 rheumatic mitral. 1 congenital heart. 1 arteriosclerotic.	8 6 rheumatic { 4 mitral P wave. 2 auricular fibrillation 1 congenital—P pattern not entirely typical. 1 arteriosclerotic—auricular fibrillation.	2 Both rheumatic—P wave pattern not abnormal.
Hypertrophy and (or) Dilation of Right Auricle	2 1 chronic cor pulmonale. 1 recent myocardial infarct.	2	0
Hypertrophy and (or) Dilation of Left and Right Auricles	10 9 rheumatic { 1 mitral. 8 mitral and tricuspid. 1 arteriosclerotic	10 9 rheumatic { 7 mitral P wave. 2 auricular fibrillation. 1 arteriosclerotic—auricular fibrillation.	0

not affect the immediate prognosis, and it usually requires less stringent management.

It was surprising that the electrocardiographic pattern of chronic coronary insufficiency did not occur in this series, except for the case in which there was an old, healed myocardial infarct. Examination of the necropsy records revealed 54 cases of coronary sclerosis without infarction; in all but four there was myocardial fibrosis of a degree which corresponded to the extent of the coronary sclerosis. In 5, complete closure of one of the main branches of the coronary vessels was found. In the 50 cases of coronary sclerosis and myocardial fibrosis the following were the electrocardiographic changes:

(a) In 9, intraventricular block (in most of these there was marked myocardial fibrosis).

(b) In 21, ventricular strain patterns, all with ventricular hypertrophy; 17 of these could be explained as a result of associated valvular lesions, pulmonary disease, or systemic hypertension, whereas, in 4, the hypertrophy of the left ventricle was unexplained unless it could be attributed to the coronary sclerosis and the consequently reduced blood supply.^{16, 17}

(c) In 20, nonspecific abnormalities.

These observations are significant because they indicate that the electrocardiogram usually does not show specific patterns in coronary sclerosis; this is an observation which we,¹⁸ as well as many others, have noted previously. Nonspecific abnormalities in the arteriosclerotic age group which are not otherwise explained should therefore be considered as evidence of coronary sclerosis.

The absence of the specific coronary pattern in coronary sclerosis and myocardial fibrosis, as well as in most instances of old, healed myocardial infarction, supports our contention⁴ that the specific S-T-T changes are primarily the result of injury to living muscle tissue, and hence evidence of coronary insufficiency.

Two of the cases of infarction deserve further mention, namely, the one of old, healed infarction, the other of recent infarction. The infarct in both cases was located on the lateral wall of the left ventricle. In the former (cf. Case 2, Table III and Fig. 6G), the limb leads showed the anterior wall pattern. In the second (Fig. 7A), the limb leads showed the anterior wall pattern but the chest leads were normal, so that the record was regarded as showing an atypical coronary contour. In neither case was the pattern like that described by Wood, et al.,¹⁹ as characteristic of lateral wall infarction, so that the interpretation of these authors may be questioned.

Acute Diffuse Pericarditis.—There were 5 cases in which this disease was diagnosed in the electrocardiogram. In 3 it was thought to be associated with recent myocardial infarction, and in 2 it was not (Table

II). In all 5 cases the lesions diagnosed in the electrocardiogram were found at autopsy. No other cases of acute diffuse pericarditis without recent myocardial infarction were found at necropsy. However, 5 cases of old, healed, diffuse pericarditis, without infarction, were encountered. As expected, in one of these there was a characteristic pattern, and, in another, there were suggestive changes; all, however, were classed as nonspecific abnormalities.

By contrast, in 2 of the 4 cases of acute diffuse pericarditis *with* recent myocardial infarction, there was electrocardiographic evidence of the recent myocardial infarction only (Table IV). These lesions were in the T stage, whereas those which were correctly diagnosed were in the S-T stage.⁸

This substantiates the deduction that acute diffuse pericarditis can be diagnosed in the electrocardiogram.⁸

Acute Cor Pulmonale.—In the one case in which this diagnosis was made from the electrocardiogram, autopsy revealed a recent, massive, pulmonary embolism (Table II). Recent, massive, pulmonary embolism was present at necropsy in 2 other cases in this series (Table IV). In one, the electrocardiogram showed a typical posterior wall infarction pattern (cf. Table III and Fig. 6II). In this case there was no S₁, Lead II resembled Lead III instead of Lead I, and T was upright instead of inverted in CF₂.²⁰ In the second case (Fig. 7B) there was intraventricular block of the second indeterminate (or S) type,²¹ which is not uncommon but not diagnostic of recent pulmonary embolism. The absence of the characteristic changes in the electrocardiogram in some cases of pulmonary embolism agrees with our previous observations.¹⁰

Chronic Cor Pulmonale.—In the three cases in which this diagnosis was made from the electrocardiogram (Table II), necropsy revealed right ventricular hypertrophy due to pulmonary emphysema. However, 5 other cases of pulmonary emphysema and right ventricular hypertrophy were found at necropsy (Table IV). In two of these there were nonspecific abnormalities and right axis shift; in two, intraventricular block of the second indeterminate (or S) type; and, in one, left ventricular preponderance (associated with hypertension). One of these patients had had auricular fibrillation, and in the others no cor pulmonale P pattern occurred. The ability to diagnose this condition is thus limited, but the characteristic pattern is diagnostic.

P-wave Patterns.—There were eleven cases in which the P pattern was of the *mitral P type* (Table II). In all of these it was presumed that the left auricle was under strain because of rheumatic mitral stenosis. In all eleven, necropsy revealed a rheumatic lesion of the mitral valve, with stenosis. In six of these cases there was involvement (dilatation and/or thickening) of the left auricle and not of the right; in the other five there was involvement of both auricles, but because of the mitral involvement the strain was presumed to be domi-

nant in the left auricle. Apparently, then, the generally accepted significance of the mitral P pattern is borne out in this series.

At necropsy, 4 additional instances of left auricular hypertrophy and/or dilatation and 5 more cases of such involvement of both auricles were encountered (Table IV). In 6 of these additional 9 cases auricular fibrillation was present (which is a common equivalent of the mitral P wave). In one of these cases, associated with congenital heart disease, the P pattern, although definitely abnormal, was not characteristic of the mitral type. In the last two cases there were no P wave abnormalities: one was a case of calcific aortic stenosis, and the other was a case of healed mitral endocarditis and massive pulmonary embolism.

Incidentally, the commonest cause of combined right and left auricular strain was the simultaneous presence of mitral and tricuspid valvular involvement (Table IV). In these instances the mitral lesion was apparently the more significant, for the mitral P wave pattern occurred in the majority. Another interesting observation was the fact that in the two cases of arteriosclerosis auricular fibrillation was present, whereas in only 4 out of 17 cases of rheumatic heart disease did this arrhythmia occur.

In five cases there was a *cor pulmonale* P wave (Table II), and in all of them there was necropsy evidence of chronic pulmonary abnormalities which might place a strain on the right auricle. However, in only two of the cases was the right auricle described in the autopsy protocol as being thickened. This accords with a previous report.²² However, in the two cases (Table IV) in which the right auricle was reported dilated and/or thickened, without involvement of the left auricle, the *cor pulmonale* P pattern was present. This is contrary to a previous report.²³ It would appear, therefore, that this pattern may be of value in detecting strain on the right auricle.

This study shows that the contour of the P wave may be of value in locating the dominant strain in the auricles in a manner similar to that employed with QRST for ventricular strain.

Nonspecific Abnormalities.—In 60 cases the abnormalities were regarded as nonspecific. This, of course, includes lesions which are not expected to give a specific pattern, instances in which lesions that are expected to give specific patterns failed to do so, and lesions which, as our knowledge advances, may come to have specific patterns associated with them. In 9 of the 60 cases of nonspecific abnormalities there were lesions at necropsy which should have produced specific electrocardiographic patterns. These are detailed in Table III and illustrated in Fig. 6J to R. They have been discussed earlier in this report, and are mentioned here again only to emphasize that heart strain and recent myocardial infarction may occasionally not be revealed in the electrocardiogram, and that old, healed myocardial infarcts often do not produce specific electrocardiographic patterns. This is true also of coronary sclerosis and myocardial fibrosis.

SUMMARY AND CONCLUSIONS

1. The electrocardiographic patterns and anatomic abnormalities in 149 consecutive autopsy cases were compared.
2. The criteria of normal and abnormal electrocardiograms are described, as well as the 12 specific electrocardiographic patterns which were encountered in this series.
3. The criteria employed in the electrocardiographic diagnosis proved to be accurate.
4. The recognition of definite patterns increases the diagnostic value of the electrocardiogram.
5. An abnormality in the electrocardiogram can be considered as objective evidence of a cardiac abnormality, but does not necessarily reveal the clinical status of the heart. The fact that the electrocardiogram is normal cannot be considered as objective proof that the heart is normal in all instances.
6. In cases of combined hypertrophy of the right and left ventricles, the electrocardiogram usually reflects only the predominant ventricular strain. Right ventricular preponderance is more often correctly diagnosed and less often overlooked than left ventricular preponderance. Marked hypertrophy, especially if both ventricles are involved, may be present without electrocardiographic evidence of ventricular strain.
7. Cases of old, healed, anterior wall infarction may be indistinguishable from cases of left ventricular hypertrophy without myocardial infarction. Conversely, left ventricular hypertrophy may give rise to an electrocardiographic pattern which is suggestive of recent anterior wall infarction.
8. The electrocardiographic pattern of congenital heart disease is diagnostic.
9. The patterns associated with recent myocardial infarction are significant, although errors both of commission and omission occur. These errors are less likely to occur when chest leads and serial curves are obtained.
10. Old, healed, myocardial infarction commonly fails to produce any characteristic electrocardiographic pattern.
11. Coronary sclerosis and myocardial fibrosis seldom give rise to any particular pattern in the electrocardiogram.
12. The electrocardiographic localization of myocardial infarction was found to be correct in this series except in one case of old, healed infarction.
13. In the two cases of lateral wall infarction which were encountered, there were anterior wall patterns in the limb leads.
14. Recent, diffuse pericarditis can be recognized in the electrocardiogram, and this is possible in the presence of associated conditions which tend to mask the pattern.

15. The patterns of acute cor pulmonale are diagnostic, but extensive, massive, pulmonary embolism may occur without these patterns. An instance of massive pulmonary embolism which closely imitated the pattern of recent posterior wall infarction is cited.

16. Chronic cor pulmonale may produce a characteristic electrocardiographic pattern which is diagnostic.

17. The cor pulmonale P wave pattern occurs in instances of dominant right auricular dilatation and/or hypertrophy, but this is not always true.

18. The mitral P wave pattern is indicative of left auricular involvement. It is an important diagnostic sign, and, in the present series, constituted electrocardiographic evidence of rheumatic heart disease.

19. The results of this study indicate that the electrocardiogram may be utilized to diagnose cardiac abnormalities and to suggest the presence of particular types of heart disease. If a conservative approach is made, the diagnostic value of the electrocardiogram justifies its present use, and this should expand as experience and critical analyses are continued.

We are indebted to Dr. O. Saphir of the Department of Pathology whose interpretations of the anatomic changes served as an important base for this study.

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DISSECTING ANEURYSM OF THE AORTA

NATHAN FLAXMAN, M.D.

CHICAGO, ILL.

A DISSECTING aneurysm is the lesion produced by penetration of the circulating blood for a varying distance between the layers of the wall of a vessel.¹ Although Fernelius² was the first to observe an aortic aneurysm and Vesalius³ the first to diagnose one, it was not until several centuries later that Maunoir⁴ clearly suggested that there may be dissection of the arterial coats by the blood. Cases of long standing, in which the blood circulates through the new sac, were first reported by Sherkelton,⁵ but Laennec⁶ was the earliest writer to use the term in a publication. Elliotson⁷ gave a clear and correct description of this condition, and Pennock,⁸ in reporting a case of long standing, demonstrated that the dissection takes place between the laminae of the media. Rokitsansky⁹ differentiated simple rupture of the aorta from dissecting aneurysm. It remained for Peacock¹⁰ to clarify the state of knowledge on this most unusual condition.

He described,¹¹ among his many cases,¹² three stages in the development of a dissecting aneurysm: (1) the incipient stage, in which there are rupture or destruction of a part or the whole of the internal coats of the vessel and extravasation of blood to a limited extent between the external and middle coats, or more probably in the laminae of the latter; (2) the early stage of a fully formed dissecting aneurysm, in which, in addition to the internal rupture, there is more extensive extravasation of blood in the coats of the vessel, separating the middle from the external tunic, or in the laminae of the middle coat for a variable distance along the aorta, and not infrequently along its primary branches, usually with external rupture into some of the adjacent cavities; and (3) the advanced stage, in which there is an opening through the internal coats leading into a sac situated within the tunics which extends along the course of the vessel and is lined by a distinct membrane very similar to the natural lining membrane of the arteries. Among the 80 cases referred to by Peacock¹³ is the first dissecting aneurysm diagnosed during life.

Fagge¹⁴ stated that if, after the first shock of the formation of the aneurysm, the patient returned to a tolerable state of health and survived for a considerable length of time, a lower communication between the sac and the aorta and some large vessel may develop. The possibility of "complete healing," with the new channel taking up part of the function of the aorta, was emphasized by Bostrom.¹⁵ Adami¹⁶ dealt only with cases of long standing, and suggested the term "arrested"

From the Cook County Hospital (Service of Dr. Harry J. Isaacs), and the Department of Medicine, Loyola University School of Medicine.

Received for publication April 8, 1942.

dissecting aneurysm in place of "healed." The important conclusions of Flockemann,¹⁷ that the dissection is probably not conditioned by disease of the vessel, and only in exceptional cases by trauma, and that, consequently, the preliminary intimal rupture is caused by overstretching of the aorta as a result of forcible action of a hypertrophied and competent left ventricle, have been generally accepted.

An outstanding contribution to this subject is that of Shenan;¹ he analyzed all of the material to 1933 (300 cases, including 17 of his own).

The present analysis of the 112 adequately studied cases¹⁸ of dissecting aortic aneurysm reported since 1933 indicates further that this syndrome, as pointed out mainly by Peacock and Shenan, is not a uniform clinical entity. Such cases do not occur frequently, and the clinical diagnosis is often difficult to establish. The rarity of such aneurysms at even large institutions may well be emphasized; only 19 cases (0.14 per cent) have been noted in 14,160 autopsies in the period from 1929 to 1941 at the Cook County Hospital. The incidence has been similarly low at the Charity Hospital of Louisiana, at New Orleans,¹⁹ and the Massachusetts General Hospital.²⁰

This report is based on the 19 patients with dissecting aneurysm of the aorta who came to autopsy at the Cook County Hospital. Although the condition was suspected in some of the cases, mainly in the few in which there was an acute onset, the diagnosis was not established clinically in any instance. There were 13 males (5 white and 8 colored) and 6 females (2 white and 4 colored); their ages varied from 22 to 70 years, with an average age of 51.8 years.

It has been the custom to classify the dissections into two types, namely, those of recent origin and the old "arrested" or "healed" aneurysms. However, a review of the literature and the analysis of the present 19 cases led to a somewhat different viewpoint. There were (1) old dissections which were (a) "silent" or (b) active, and (2) recent dissections which were (a) typical or (b) atypical. Such a viewpoint, bearing in mind that it is possible to have four completely different clinical pictures of dissecting aneurysm of the aorta, may help in the diagnosis and prognosis of this condition. The main reason for expressing this view is the fact that the average duration of life with the old dissections was 3 years, whereas, with the recent ones, it was only 17.6 days.

OLD, "SILENT" DISSECTIONS

In these 12 cases there was a gradual onset of symptoms and signs of congestive heart failure. None of the 12 patients had a history of excruciating pain in the chest radiating into the neck, the back, or the abdomen. In four of these cases, in addition to the congestive failure, the physical and roentgenologic observations led to a diagnosis of syphilitic aortic aneurysm. The outstanding feature of these old, "silent" dissections was the intractable heart failure, and the following cases illustrate the important abnormalities.

CASE 2.—L. F., a white man, 55 years old, first entered the hospital on February 16, 1930. He complained only of dyspnea, cough, and weakness of two months' duration. Physical examination revealed a very dyspneic patient who had a blood pressure reading of 240/160, impaired resonance and moist râles at the bases of both lungs, and a transverse cardiac measurement of 18 cm. The only laboratory data of note were the Wassermann reactions on the blood and spinal fluid, both of which were moderately positive (2 plus). With absolute rest in bed and digitalis he responded slowly, but not well, and he left the hospital at his own request on March 5, 1930. He re-entered April 30, 1930, complaining of marked weakness, a loss of 20 pounds in weight, and hemoptysis, in addition to dyspnea and cough. The physical signs were completely altered. There was a difference in the blood pressure in the two arms; on the left it was 148/52, and, the right, 122/52. There was a marked difference in the radial pulses; the right was scarcely palpable, and the left was water-hammer in character. The heart was enlarged (transverse diameter, 22 cm.), and systolic and diastolic murmurs were audible over the aortic area. A pistol-shot sound was heard over the femoral arteries. Dullness and moist râles were present over the bases of both lungs. The Wassermann reactions on both the blood and spinal fluid were again moderately positive. Roentgenologic examination of the chest, which had previously revealed only an enlarged heart, now showed a diffuse enlargement of the aortic shadow. The symptoms became steadily worse, and the patient attempted suicide by cutting his wrists. Death occurred May 20, 1930, as a result of infection of the self-inflicted lacerations. Autopsy (by Dr. Phillip Shapiro) revealed (1) an ancient dissecting aneurysm of the arch of the aorta, with rupture two fingerbreadths above the valve and return rupture at the junction of the transverse and descending portions, (2) a double tube in the arch of the aorta which extended into the innominate and the left common carotid arteries, (3) atheromatosis of the aorta, (4) eccentric hypertrophy of the heart, which weighed 700 grams, with dilatation of the left ventricle, (5) chronic passive congestion of the lungs, liver, kidneys, spleen, and gastrointestinal mucosa, and (6) acute infectious splenic tumor.

CASE 3.—B. J., a white man, 50 years old, first entered the hospital February 15, 1930, complaining of dyspnea of one year's duration. The only abnormalities were moist râles at the bases of both lungs, a blood pressure of 260/150, a transverse cardiac measurement of 15 cm., and a rough systolic murmur at the apex. He responded slowly and poorly to treatment with digitalis. Between the first admission and his final entrance into the hospital 19 months later, he was hospitalized on six other occasions, each time for a longer stay. He was markedly decompensated and edematous when he re-entered for the last time on October 7, 1931. Physical examination revealed a very cyanotic, orthopneic, and poorly nourished man. The blood pressure in both arms was 210/120. The transverse diameter of the heart was enlarged to 19 cm., and there was an irregularity of rate and rhythm. General anasarca was present. Laboratory examination was negative except that the urine showed 2+ albumin and many hyaline casts. He grew steadily worse, but with absolute rest in bed he lived until February 16, 1932, three years after the onset of the first symptom and two years after he was first hospitalized. Autopsy (by Dr. Victor Levine) revealed (1) an ancient dissecting aneurysm of the descending aorta and marked atheromatosis of the aorta, (2) thrombosis of the lower end of the newly formed lumen of the aorta, (3) an ancient fibroplastic deformity of the aortic valve, with moderate stenosis and insufficiency, and a recent verrucous endocarditis of the mitral valve, (4) marked eccentric hypertrophy of the heart, which weighed 540 grams, (5) chronic passive congestion of the lungs, kidneys, and spleen, (6) chronic passive congestion of the liver, with early cardiac cirrhosis, (7) arteriosclerosis of the kidneys, and (8) hydrothorax, hydropericardium, and ascites.

OLD, "ACTIVE" DISSECTIONS

There were four patients with old dissections, but the lesions were "active" throughout. Except for the history, the clinical manifestations varied little from those in the cases of old, "silent" dissections. The history was one of repeated attacks of pain in the chest, neck, and back over a period of weeks or months, until a final excruciating attack was experienced.

CASE 13.—M. P., a colored woman, 50 years of age, entered the hospital October 15, 1934. She stated that she was well until six months before entry, when she began to have severe attacks of pain in the front of the chest that went up into the neck and through to the back. At first the attacks lasted only a few minutes, but each successive one lasted a little longer, and she became short of breath. Six hours before admission she experienced an attack of excruciating pain in the chest that radiated in the manner described. The pain persisted and dyspnea became very marked. On physical examination she appeared very ill. The blood pressure was 152/64 in both arms. The left border of the heart was 13 cm. from the midsternal line, and loud, rough, systolic and diastolic murmurs were audible at the aortic area. The pulse was water-hammer in character. Laboratory examination was negative. Her pain increased; she grew worse steadily, and died October 18, 1934. Autopsy (by Dr. Frank B. McJunkin) revealed (1) a dissecting aneurysm (not recent) of the aorta, with extension of the dissection into both common iliac arteries and the innominate artery, and rupture into the pericardial sac, (2) hemopericardium (250 c.c.), (3) atherosclerosis of the aorta, (4) bilateral hydrothorax, and (5) passive congestion of the viscera.

CASE 14.—A. C., a white woman, 69 years old, entered the hospital June 30, 1937. In February, 1937, she had an attack of "grippe," and was then well until April, 1937, when, on trying to open an umbrella against the wind, she had an attack of severe pain in the chest and a sensation as if she were choking to death. She had four similar attacks that day, and another at 4 A.M. the next day which was brought on by arising. Thereafter she stayed in bed under medical care, but the attacks continued, and the pain radiated into the neck and the back. She became increasingly short of breath. Physical examination on admission to the hospital, three months after the initial attacks of pain, revealed a very acutely ill woman. The blood pressure in both arms was 140/60. There were moist râles at the bases of both lungs. The apex beat was diffuse, heaving, and irregular. The left border of the heart was 15 cm. from the midsternal line. Systolic thrills were palpable over the apex and the base of the heart, and the heart tones were harsh. A rough systolic murmur was audible over the apex. The rate and rhythm were grossly irregular. She became steadily worse, and died July 26, 1937. Autopsy (by Dr. Ben W. Lichtenstein) revealed (1) a dissecting aneurysm (not recent) of the ascending portion and arch of the aorta, with rhexis at three points, (2) slight hypertrophy of the heart, which weighed 350 grams, (3) severe atherosclerosis of the aorta, (4) bilateral hydrothorax, and (5) passive congestion of the lungs, liver, and spleen.

RECENT DISSECTIONS

Three patients had recent dissecting aneurysms of the aorta, but in only two was there the so-called typical clinical picture. One patient had excruciating chest pain, and the other collapsed suddenly. In both cases the clinical diagnosis was coronary thrombosis, the condition with

TABLE
ESSENTIAL DATA ON NINETEEN AUTOPSY

CASE	SEX	COLOR	AGE	TYPE	DURATION	MURMURS	EKG.	SYPHILIS
1	M	C	56	Old silent	5 years	None	LAD*	-
2	M	W	55	Old silent	6 months	Systolic-diastolic at aortic area	LAD	+
3	M	W	50	Old silent	3 years	Systolic at apex	A.F.†	-
4	M	W	51	Old silent	2 years	Systolic at apex	LAD, T ₁	-
5	M	C	50	Old silent	2½ years	Systolic-diastolic at apex and base	LAD	-
6	M	C	70	Old silent	1 year	Systolic-diastolic at apex and base	LAD	-
7	M	C	51	Old silent	1 month	Systolic-diastolic at apex	LAD	-
8	M	C	31	Old silent	3 years	Systolic-diastolic at apex and base	BBB‡	-
9	M	C	62	Old silent	2 years	Systolic-diastolic at apex and systolic at base	A.F.	+
10	F	C	55	Old silent	5 years	Systolic-diastolic at base	LAD	-
11	F	C	53	Old silent	10 years	Systolic-diastolic at base	LAD	-
12	M	W	52	Old silent	3½ years	Systolic at apex and base	LAD	+
13	F	C	50	Old active	6 months	Systolic-diastolic at base	LAD	-
14	F	W	69	Old active	4 months	Systolic at apex	A.F.	-
15	F	C	40	Old active	?	Systolic-diastolic at aortic area	None	-
16	M	C	67	Old active	?	None	None	-
17	M	C	67	Recent typical	36 days	Systolic at apex	LAD, T ₁ , T ₂	-
18	F	W	55	Recent typical	6 days	Systolic at aortic area	None	-
19	M	W	22	Recent atypical	11 days	Systolic-diastolic at apex and base	LAD	-

*Left Axis Deviation.

†Auricular Fibrillation.

‡Bundle Branch Block.

I

CASES OF DISSECTING ANEURYSM OF THE AORTA

CLINICAL DIAGNOSIS	AUTOPSY FINDINGS		
	HEART DISEASE	HEART WEIGHT	CAUSE OF DEATH
Hypertensive Heart Disease	Hypertensive	825 Gm.	Rupture of ascending aorta
Hypertensive and Luetic Heart Disease and Aneurysm	Hypertensive and Luetic Aortitis	700 Gm.	Septicemia
Hypertensive Heart Disease	Hypertensive and Coronary	540 Gm.	Thrombosis of newly formed aorta
Hypertensive Heart Disease	Hypertensive	890 Gm.	Rupture of ascending aorta
Luetic Heart Disease	Hypertensive and Coronary	690 Gm.	Rupture of ascending aorta
Multiple Aneurysmal Dilatation of Aorta	Coronary and Hypertensive	510 Gm.	Empyema
Hypertensive Heart Disease	Hypertensive	565 Gm.	Congestive Heart Failure
Luetic Heart Disease	Hypertensive	810 Gm.	Rupture of ascending aorta
Luetic Heart Disease	Luetic, Hypertensive, and Coronary	625 Gm.	Rupture of ascending aorta
Luetic Heart Disease	Hypertensive	450 Gm.	Rupture into pericardial sac
Hypertensive and Luetic Heart Disease	Coronary and Hypertensive	480 Gm.	Pulmonary embolism
Aortic Aneurysm	Hypertensive and Luetic	720 Gm.	Congestive Heart Failure
Luetic Heart Disease	Hypertensive and Coronary	500 Gm.	Rupture into pericardial sac
Coronary Heart Disease	Coronary and Hypertensive	350 Gm.	Rupture, ascending and arch of aorta
Luetic Heart Disease	Hypertensive	550 Gm.	Rupture into pericardial sac
Left Lower Lobar Pneumonia	Hypertensive and Coronary	700 Gm.	Rupture into pericardial sac
Coronary Thrombosis	Hypertensive and Coronary	550 Gm.	Rupture of ascending aorta
Coronary Thrombosis	Hypertensive	450 Gm.	Rupture into pericardial sac
Aortic and Mitral Endocarditis, with rupture of aortic leaflet	Hypertensive	590 Gm.	Multiple ruptures (5) of aorta

which dissecting aneurysm is most commonly confused. The two cases were as follows:

CASE 17.—G. A., a colored man, 67 years old, entered the hospital November 20, 1932. He had been well until the day before admission, when he was suddenly seized with excruciating pain in the epigastric region. He vomited twice at the onset, but got no relief. The pain persisted. The only other significant fact in the history was that, 3 years earlier, one of his legs had been amputated because of gangrene secondary to atherosclerotic occlusion of the popliteal artery. The blood pressure was 184/104 in both arms, the left border of the heart was 11 cm. from the mid-sternal line, and the heart tones were soft and muffled; a rough, blowing, systolic murmur was audible over the base of the heart. The percussion note over the base of the left lung was flat, and no breath sounds could be heard over the area of flatness. Roentgenologic examination of the chest on November 23 showed a widening of the aortic arch suggestive of aneurysm. With absolute rest in bed the pain disappeared, and he seemed to be recovering, but died suddenly on December 16, 1932, twenty-six days after the onset of the severe pain. Autopsy (by Dr. Victor Levine) revealed (1) a recent dissecting aneurysm of the aorta, with rupture at the level of the obliterated ductus arteriosus and just above the bifurcation, (2) perforation of the dissecting aneurysm near the attachment of the ductus arteriosus into the peri-aortic and mediastinal fat, (3) extension of the hemorrhage from the mediastinal fat into the left pleural cavity, with the formation of an encapsulated hematoma containing 1000 c.c. of liquid blood, (4) marked eccentric hypertrophy of the heart, which weighed 550 grams, (5) marked sclerosis of the base of the aortic valve, (6) moderate sclerosis of the aorta and the coronary and iliac arteries, and focal medionecrosis of the aorta, (7) atheromatosis of the mesenteric and subelavian arteries, and (8) arteriosclerosis of the kidneys, with cyst formation.

CASE 18.—L. S., a white woman, 55 years old, entered the hospital April 11, 1940. While at work on the morning of the day of entry, she suddenly collapsed and had involuntary urination and defecation. On entrance, several hours later, it was noted that she spoke with difficulty and could not move either the upper or lower extremity on the right side. She had no pain. Physical examination revealed an ashen color of the face, a questionable blood pressure reading of 110/70, no perceptible pulse on the right and a palpable pulse on the left side, extension of the left border of the heart 12 cm. from the midsternal line, faint heart tones, with a rough systolic murmur over the aortic area, and paresis of the right upper and lower extremities. By the third hospital day she had improved considerably; she had a full pulse in both extremities, normal speech, and a complete return of function in the right arm and leg. The patient was feeling good, but died suddenly on the fifth hospital day, April 16, 1940. Autopsy (by Dr. William P. Mavrelis) revealed (1) a dissecting aneurysm of the arch and descending and abdominal aorta, (2) rupture of the ascending arch, with a hemopericardium of 250 c.c. of blood tinged fluid and 450 grams of clotted blood, (3) extension of the dissecting aneurysm into the innominate, the left common carotid, and both the subelavian and iliac arteries, (4) thrombosis of the dissecting sacs of the innominate and left common carotid arteries, with compression of their lumina, (5) aneurysmal outpouching of the ascending arch of the aorta, (6) marked eccentric hypertrophy of the heart, which weighed 450 grams, (7) marked coronary sclerosis, (8) marked passive congestion of the liver and kidneys, and (9) benign nephrosclerosis.

In addition to the absence of pain and collapse and the comparative youth of the patient, the other case of recent dissection was atypical in other respects.

CASE 19.—L. S., a 22-year-old white man, was admitted to the hospital January 21, 1940. A week before entrance he contracted an acute upper respiratory infection which was accompanied by a persistent, productive cough. On the day before

admission, while sitting up in bed, he suddenly developed severe shortness of breath and extreme weakness. Even in the upright position he could hardly breathe. There was no pain or hemoptysis. The history was negative for previous dyspnea, palpitation, and edema, but it was later learned that his brother, 27 years old, was under treatment at another hospital for "high blood pressure" and "heart trouble." The patient was extremely dyspneic and orthopneic, and severely ill. The blood pressure in both arms was 114/48. The left border of the heart was 13 cm. from the midsternal line. Loud, harsh, systolic and diastolic murmurs were audible at the apex and base of the heart. A systolic thrill was palpable over the right carotid artery. He had a very stormy course, heavy doses of morphine notwithstanding, and died four days after admission to the hospital (January 25, 1940). Autopsy (by Dr. A. C. Bach) revealed (1) a dissecting aneurysm, with multiple tears of the ascending portion, the arch, and the abdominal portions of the aorta, (2) marked eccentric hypertrophy of the heart, which weighed 590 grams, with very marked dilatation of all cardiac chambers, (3) marked dilatation of the aortic valve, with insufficiency, (4) edema of all pulmonary lobes, (5) partial occlusion of both coronary ostia by the dissecting aneurysm, (6) passive congestion of the liver and spleen, (7) ascites, and (8) moderate bilateral hydrothorax and hydropericardium. There was no evidence of inflammation; the media of the aorta showed only marked fibrosis.

COMMENT

Previous to 1933, the diagnosis of dissecting aneurysm of the aorta had been made during life in only seven cases. Since that time the ante-mortem diagnosis has been made in 25 additional instances, bringing the total to 32 (7.9 per cent) out of 431 reported dissections. In the cases in which a diagnosis was made during life there were certain suggestive manifestations that pointed to the lesion. Among these were (1) a sudden onset of severe tearing or crushing pain, usually thoracic, reaching its maximum intensity at once in a person with a history of hypertension; (2) wide but variable radiation of pain to the neck, head, back, abdomen, or lower extremities, or to all of these, but rarely to the arms; (3) moderate to extreme collapse, even though the blood pressure was maintained for some time at a high level; (4) a rapid, enlarged heart; (5) a rapid change in the roentgenologic appearance of the aortic shadow; and (6) patchy and bizarre neurologic changes in the legs.

Dissecting aneurysm of the aorta is often confused with coronary thrombosis,^{21, 22} and is considered first in the differential diagnosis.²³ It must be remembered that the dissection may invade the root of the aorta, as well as the first portion of a coronary artery; the resulting ischemia may produce acute myocardial infarction, with typical electrocardiographic changes.²⁴ Extravasation of blood may also occur, and the resultant electrocardiographic changes are characteristic of coronary occlusion.²⁵ Syncope has already been emphasized as an important clinical feature at the onset of the dissection,^{26, 27} and as an aid in the differential diagnosis from coronary thrombosis.²⁵

Maintenance of hypertension through the course of the illness, or for some time at a high level,²⁷ has been considered an important feature, but Hamburger and Ferris²⁵ recorded this in only one of their six recent

cases. Gouley and Anderson²⁸ noted particularly the associated aortic murmurs of chronic dissections which simulate those of syphilitic cardiovascular disease. The cardiac hypertrophy may increase very rapidly after the dissection.^{27, 28} The icterus index may be elevated as long as two weeks after the onset of the dissection.³⁰

As with aortic insufficiency, the earliest tendency was to attribute the lesion to strain on the heart or even direct trauma; the latter was quite common, but with recognition and acceptance of the fact that syphilis may cause such a lesion, the opinions swung to the other extreme.³¹ A middle course is now followed, as syphilis is generally absent in the majority of cases.³² However, even in the presence of a syphilitic aneurysm of the aorta, acute dissection can occur independently.²⁴ In the old, "silent" cases, the dissecting aneurysm may readily be confused with one of syphilitic origin.^{20, 28, 33} Patchy and bizarre neurologic changes in the legs which occur as the result of circulatory deficiencies in the spinal cord caused by rupture of the intercostal and lumbar arteries are of great importance.^{34, 35}

"Healed" or "arrested" dissecting aneurysms may allow the patient to survive for months or even years. The patient is not out of danger even when he has survived the dissection, for the "healed" channel is still prone to complete rupture as a result of imperfections in its walls.³⁶ One of Rogers' patients lived 27 months after the acute attack,³⁴ and Roberts³⁷ was of the opinion that the aneurysm in one of his cases had formed about three years before death. East³⁸ followed his patient, a 43-year-old white woman, from the first typical symptoms of dissecting aneurysm to her sudden death from rupture of the newly formed sac five years later.

Weiss, Kinney, and Maher³⁹ reported three cases that were unusual, not only because the dissecting aneurysm was completely "healed," but also because atherosclerosis was present in the new channel in the wall of the aneurysm. The biggest dissecting aneurysm on record, which occurred in a 15-year-old white male with a negative past history, was described in 1939;⁴⁰ the dissection affected the whole aorta and its main branches, and the process extended into the lower limbs as far as the popliteal artery on the left and the posterior tibial in the lower third of the leg on the right. There was also dissection of the pulmonary artery and its main branch; this had not been previously described. Only one case of coarctation of the aorta with a terminal dissecting aneurysm⁴¹ has been reported since 1933, which brings the total of such cases to 14. In the period covered at the Cook County Hospital, namely, from 1929 to 1941, there was one patient with coarctation of the aorta with rupture who came to autopsy, but no dissecting aneurysm was present.

SUMMARY

The clinical aspects and the post-mortem observations in 19 cases of dissecting aneurysm of the aorta are described. Clinically, these pa-

tients presented (1) old dissections, with intractable heart failure, which had (a) a "silent" history and course in regard to the dissection, or (b) an active history and course, with repeated attacks of severe pain in the chest that radiated into the neck and back; and (2) recent dissections with (a) a typical onset of pain or collapse and (b) an atypical onset with severe dyspnea.

Physical signs of a variable character, such as cardiac murmurs, were outstanding, and did not conform to any definite pattern. The majority of patients with dissecting aneurysm of the aorta do not have a typical onset or course; the latter may extend over many months, but at some time present any or all of the physical signs which have been discussed.

NOTE: Since this article was submitted for publication, two excellent discussions on the subject have appeared:

Sailor, S.: Dissecting Aneurysm of the Aorta, *Arch. Path.* 33: 704, 1942.

Mote, C. D., and Carr, J. L.: Dissecting Aneurysm of the Aorta, *AM. HEART J.* 24: 69, 1942.

Each article represents a different aspect, the former on the pathology, and the latter on the medicolegal viewpoint.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING ELECTRICALLY INDUCED CONVULSIONS

EDWARD M. KLINE, M.D., AND JOSEPH L. FETTERMAN, M.D.
CLEVELAND, OHIO

SINCE the publication of our report dealing with the electrocardiographic changes following metrazol-induced convulsions,¹ a new type of convulsant² has been introduced for the treatment of certain psychoses. In this method a convulsion is produced by passing a high frequency alternating current between electrodes placed on either temple.* We refer to this technique as electro-coma therapy.

Certain advantages of this method, such as ease of administration, more uniform reaction, and less violent convulsions, suggest that this form of treatment will largely replace metrazol. For this reason it seemed worth while to repeat our observations before and after electrically induced convulsions, and to compare them with those which occurred when metrazol was used as the convulsant agent.

Forty-two patients from the private psychiatric practice of one of us (J. L. F.) were selected for this study. All were suffering from major psychoses; depressions were the most common because of their favorable response to this form of therapy. The ages ranged from 19 to 71; the distribution by decades is shown in Table 1.

Electrocardiographic observations were made on each patient before and after a major convulsive seizure (lasting from 30 to 50 seconds). The three standard leads of the electrocardiogram were taken just preceding the application of the current, and Lead II was again recorded immediately upon cessation of the convulsion, and at three, five, and ten minutes after the electric shock. Later in our study, a single apex lead was employed in addition to those mentioned above.

CHANGES IN BLOOD PRESSURE

Blood pressure measurements were made coincidentally with the electrocardiograms whenever the patient's cooperation would permit. In all but one instance there was a rise in the systolic pressure, and this was usually accompanied by a smaller increase in the diastolic. The mean increases were 30 mm. Hg for the systolic, and 9 mm. Hg for the diastolic.

CHANGES IN HEART RATE

An acceleration in cardiac rate was encountered in nearly all instances. If an arbitrary figure of twenty-five cycles per minute is

From the Department of Medicine of Western Reserve University School of Medicine, and the Lakeside Hospital, Cleveland.

*The instrument employed in this work was manufactured by Offner Electronics Corporation, Chicago, Illinois. In this machine the "dosage" may be varied by a change in the intensity of the current and the duration of its action. The maximum intensity is 100,000 cycles per second, and the time range from 0.05 to 1.0 second. In all cases the "dose" is ascertained by starting below the ordinary convulsant dose and increasing either the time or intensity. This minimum "dose" is continued or increased slightly throughout the course of treatments.

Received for publication April 8, 1942.

TABLE I
AGE DISTRIBUTION IN DECADES

Age in years	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Number of cases	2	5	12	11	6	5	1

TABLE II
CHANGES IN BLOOD PRESSURE

CASE NO.	CONTROL	IMMEDIATELY AFTER CONVULSION	3 MIN. AFTER SHOCK	5 MIN. AFTER SHOCK	10 MIN. AFTER SHOCK
1.	105/75	140/75	105/60		100/70
2.	120/80	150/90			
3.	150/80	210/90		140/70	145/75
4.	120/80	160/80			
5.		120/70	145/95	120/65	
6.	150/95	185/100	155/85		145/80
7.	125/100	150/105			
8.	130/90	155/95	135/95		125/90
9.	165/105	215/110	210/100	180/100	180/110
10.	120/80	140/85	130/80		110/80
11.	120/80	130/90			135/90
12.	120/80	140/75		125/75	120/70
13.	125/80	140/85	140/85		125/60
14.	130/80	135/80	135/85	130/80	
15.	145/80	210/100		170/80	
16.	135/90	145/75		140/80	130/70
17.	140/80	140/90	145/75	130/70	135/60
18.	115/70	120/75	135/70		120/75
19.	135/80	150/90	145/95	140/90	140/90
20.	130/75	170/90		150/85	
21.	120/75	140/90		140/70	
22.	160/85	180/90	160/90		130/70
23.	140/80	160/90		150/90	150/80
24.	135/80	165/80	160/90		145/75
25.	140/75	160/90		150/95	140/80
26.	110/60	135/70		130/75	125/75
27.	115/70	150/80		130/80	120/70
28.	110/50	140/90	160/80	135/70	110/60
29.	130/80		160/90	160/90	110/70
30.	120/80	150/90	135/60		110/70
31.	115/60	170/90		140/80	135/75
32.	130/70	180/70		140/70	130/60
33.	140/90	180/100	190/110		130/80
34.	130/80	170/90	150/80	140/75	115/70
35.	120/70	160/80	130/70		110/65
36.	110/70	140/60		110/60	
37.	110/80	130/70		130/50	
38.	160/90	180/80		130/70	120/80
39.	160/100	180/?		150/100	155/100
40.	155/80	240/120	190/90	175/90	190/80
41.	135/85	170/100	180/80	150/80	150/85
42.	120/80	125/80	130/80	125/70	80/50

assumed to constitute a significant change, there were only ten cases in which the rate was not increased by this amount, and in only one was there a decrease. This is in contrast with the rates after metrazol therapy, when no consistent change occurred. Furthermore, there were none of the extremely slow rates; the single bradycardia was of nodal origin, with a rate of 58 per minute.

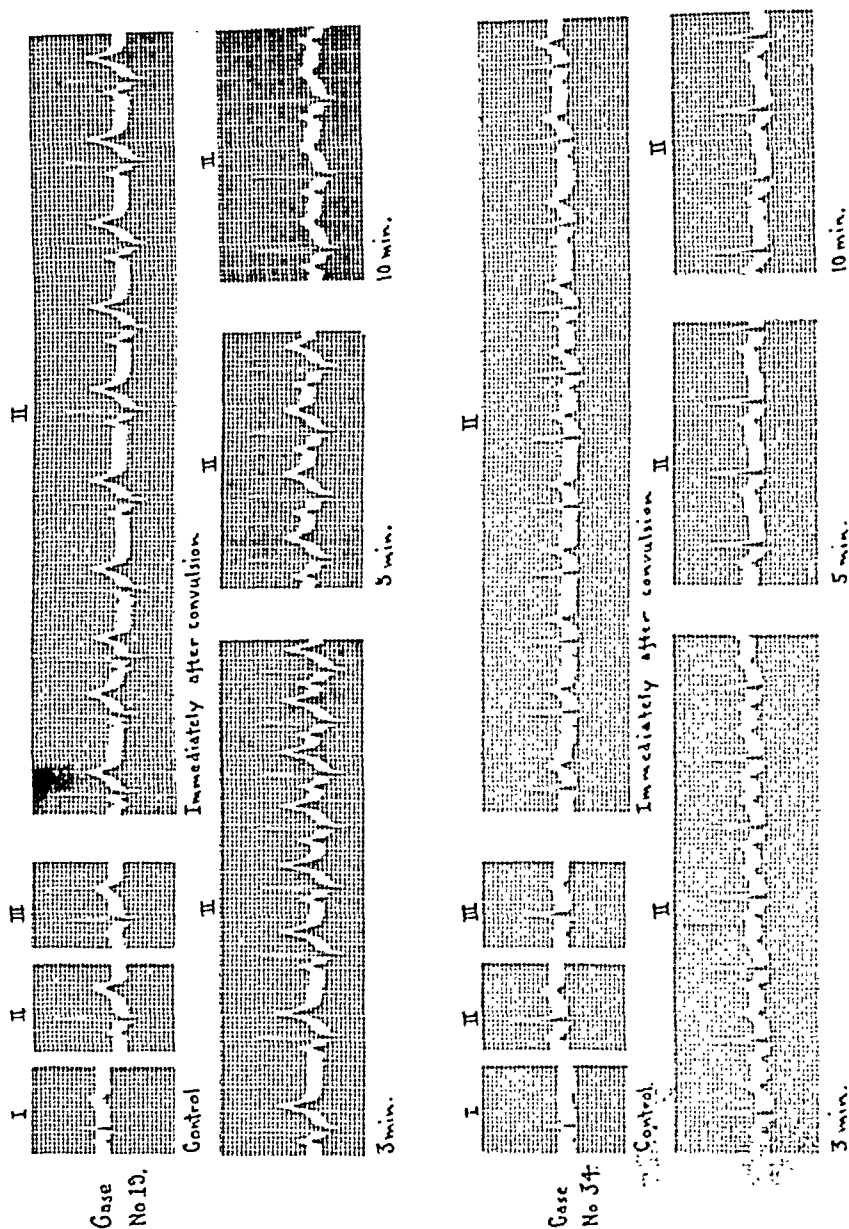


Fig. 1.—Case 19. Nodal rhythm immediately after the convulsion. Note the change in the amplitude and contour of the T wave.
Case 34. Shifting pacemaker immediately after the convulsion.

CHANGES IN RHYTHM

Contrary to the situation after metrazol convulsions, cardiac arrhythmias were not conspicuous. Although there was some change in cardiac rhythm (Fig. 1) in fifteen of the cases, in only two instances was the arrhythmia of a gross nature. These changes were usually present in the record taken immediately after the convulsion, and in all instances the rhythm had returned to normal in the 5-minute record. It can be seen from Table III that the arrhythmias were of two types: those produced by changes in the heart rate and location of the pacemaker; and those resulting from extrasystoles of various types.

TABLE III
TYPE AND FREQUENCY OF ARRHYTHMIAS

TYPE	NO.
Sinus arrhythmia (marked)	2
Shifting pacemaker	4
Atrioventricular rhythm	3
Auricular extrasystoles	7
Atrioventricular extrasystoles	1
Ventricular extrasystoles	2
Number of convulsions after which the above observations were made	15
Number of convulsions after which no significant arrhythmia was observed	26

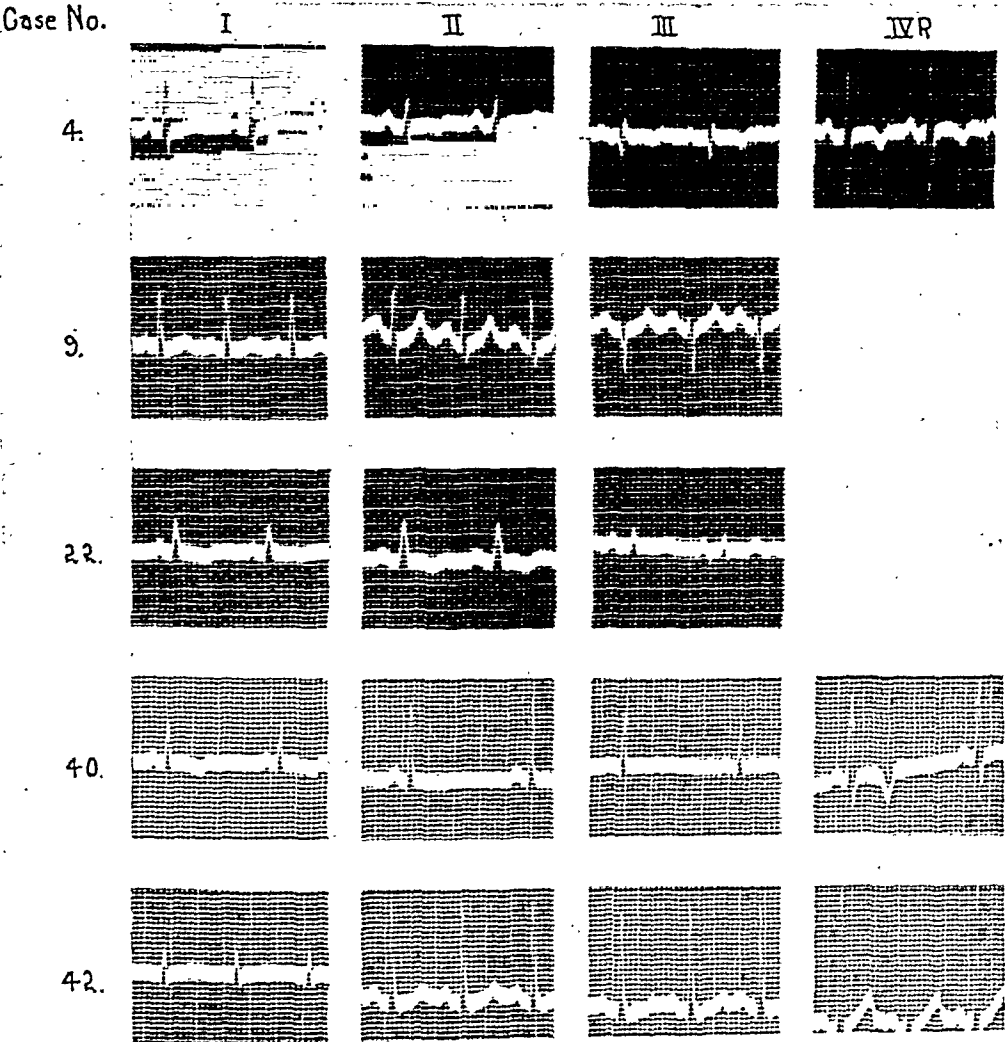


Fig. 2.—Electrocardiograms in the cases in which the cardiovascular system was abnormal.

We cannot say definitely from these observations what mechanism is responsible for the alterations in rhythm. It seems probable that the changes in the location of the pacemaker were the result of vagal stimulation induced by the sharp rise in blood pressure which occurred in most instances.

CHANGES IN THE T WAVE

An increase in the amplitude of the T wave was encountered in all but eight of the cases. This increase in height was accompanied by a change in contour; the wave became more pointed, and narrow at the base. These resembled the T waves after metrazol-induced convulsions. Since these changes are similar to those which occur in acidosis,³ the possibility exists (as in the case of metrazol) that there is a temporary acidosis immediately after the convulsion. This might be produced by the extreme muscular activity during a period when respiration is diminished or absent. Contrary to the observations of Bellet⁴ and his associates, we had no instances in which the T wave became inverted, or the S-T segment significantly elevated, after treatment.

CASES IN WHICH THE CARDIOVASCULAR SYSTEM WAS ABNORMAL

There were five cases in this series in which the cardiovascular system was abnormal. In three cases, Nos. 9, 22, and 40, the patients had hypertension, and their electrocardiograms are shown in Fig. 2. Case 4 was that of a fifty-five-year-old woman who had had angina pectoris for many years, in whom Dr. Claude Beck had established a collateral coronary bed by operation on July 30, 1937. In each of these patients the critical nature of the mental condition was such that the risk of treatment seemed justified. All were given the usual course of seizures without complication, and the electrocardiograms after treatment did not differ from those of other patients in this series. In this group we were particularly interested in knowing whether the convulsion might not be followed by a period of myocardial anoxemia. Our attention was, therefore, directed to the S-T segment in the standard and apex leads, but in no instance were these significantly altered.

Case 42 was that of a fifty-eight-year-old man with chronic valvular disease of rheumatic origin. He had mitral stenosis and insufficiency and moderate cardiac enlargement, but there were no signs of cardiac failure. This patient's mental illness was extremely severe. He refused all food, and, in spite of forced feedings, he lost seven pounds in weight during his first week in the hospital. Twenty minutes after the patient's first convulsion he perspired profusely, and became pale, cold, and clammy. The blood pressure, which, during the treatment, had been in the neighborhood of 125/80, fell at this time to 70/30. He was given 0.5 Gm. of caffeine citrate and two 0.3 c.c. doses of adrenalin hydrochloride (1:1,000 dilution). In another twenty minutes the blood pressure had returned to its former level and he appeared normal again. The electrocardiogram at this time was identical with the control record, taken before the seizure had begun. This reaction was different from anything we had seen before, and cannot be satisfactorily explained. Whether the peripheral vascular collapse was associated in some manner

with the cardiac lesion cannot be stated with certainty, but it seems rather unlikely. No late untoward results have developed, but treatment was not resumed.

CONCLUSIONS

The electrically induced convulsion was followed by a rise in both the systolic and diastolic blood pressure, an increase in heart rate, and certain transitory electrocardiographic changes. The T waves of the electrocardiogram were increased in amplitude, and, in some cases, a change in rhythm was observed. These alterations in the cardiovascular system were less marked than those which occurred after metrazol-induced convulsions.

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STUDIES ON CORONARY OCCLUSION

III. THE EFFECT OF DIGITALIS ON THE RS-T SEGMENT OF THE ELECTROCARDIOGRAM AFTER CORONARY LIGATION

MICHAEL G. MULINOS, M.D., AND ALAN LESLIE, M.D.
NEW YORK, N. Y.

DIGITALIS should not be used in coronary artery disease unless there is heart failure which has not responded to any other treatment.¹⁻⁸ There are three principal reasons for this. First, digitalis increases myocardial irritability; consequently, a dangerous or fatal ectopic rhythm may result from a further increase of myocardial irritability in a heart which already has an abnormally irritable focus in the areas of infarction. Secondly, digitalis increases the strength of the cardiac contraction; this would increase the danger of dislodging mural thrombi after occlusion. Furthermore, the resultant rise in intraventricular pressure may cause aneurysmal dilatation of the infarcted ventricle, or may increase any already existing dilatation. Thirdly, digitalis is believed to cause constriction of the coronary arteries. The constriction may occur both directly, by the smooth muscle action of digitalis, and indirectly, through nervous impulses mediated by way of the centrally stimulated vagus.

The question whether digitalis actually does produce coronary artery constriction has been extensively investigated, both experimentally and clinically. Suggestive of coronary spasm are the attacks of thoracic oppression after overdosage with digitalis in patients treated for cardiac failure.³ In animal experiments, Meyer⁹ and Sakai and Saneyoshi¹⁰ found that digitalis did not constrict the coronary vessels in situ. As a result of these studies, Eggleston¹¹ advanced the now prevalent opinion that digitalis is not contraindicated in cases of cardiac failure complicated by angina. Gold, et al.,¹² found that digitalis did not differ from placebos in its effect on cardiac pain. From this they concluded that "... digitalis even in large doses rarely, if ever, produced effective constriction of the coronary arteries in man." Bond¹³ measured coronary vein outflow in dogs, and found that digitalis was without effect. Using a Starling heart-lung preparation and a Morawitz cannula, Bodo¹⁴ observed increased flow after digitalis, and concluded that digitalis actually dilated the coronary vessels. Fenn and Gilbert¹⁵ found that, in dogs, digitalis caused a decrease in coronary sinus outflow. The effect did not appear after section of the vagi. Voegtlin and Macht¹⁶ observed contraction of isolated rings of ox and pig coronary arteries in response to certain digitalis bodies, but relaxation after certain others.

From the Department of Pharmacology, College of Physicians and Surgeons, Columbia University.

Received for publication April 22, 1942.

They recommended the administration of nitrites along with digitalis in those cases in which coronary constriction must be avoided. Ginsberg, Stoland, and Siler¹⁷ used various commercial digitalis preparations on intact dogs and in heart-lung preparations (Morawitz cannula). Their results were inconsistent, more so in the intact animal than in the heart-lung preparation. They formed the opinion that coronary constriction, if it occurs after digitalis administration, is not of sufficient degree to constitute a contraindication to the drug in any but cases of severe coronary insufficiency. Essex and his associates,^{18, 19} using the thermostromuhr, observed no change in the coronary blood flow in dogs as a result of administering the digitalis glycosides. Haskell, et al.,²⁰ found that, as compared to cats, dogs were poor subjects to use in digitalis studies because of their inconsistent reaction to this drug. Therefore, results obtained with digitalis on the dog must be interpreted with caution. Routier and Puddu²¹ stated that the changes in the T wave which they observed were not due to an effect of digitalis upon the coronary vessels because, in cases of coronary artery disease, digitalis did not exaggerate the electrocardiographic changes produced by effort. In 1941, Liebow and Feil²² stated that "the effect of this drug [digitalis] on the coronary arteries is still not known."

From this confusing mass of clinical and experimental material and opinion, it is impossible to arrive at any satisfactory conclusion concerning the effects of digitalis on the coronary arteries. It is the purpose of the data herein presented to cast further light on this problem from a somewhat different experimental approach.

The authors^{23, 24} demonstrated that, after coronary ligation in cats, the induction of generalized anoxemia increased the RS-T segment deviation of the electrocardiogram, probably because the induced anoxemia increased the local myocardial anoxia caused by the ligation. Levy and his co-workers²⁵ obtained similar reactions in cases of human coronary insufficiency, and accorded diagnostic value to the changes in the T wave which occur during induced anoxemia. The only consistent results obtained by us were changes in the RS-T segment deviation. The reaction to induced anoxemia suggested a new approach to the problem of how digitalis affects the coronary circulation. *If, after coronary artery ligation, a drug increases the deviation of the RS-T segment of the electrocardiogram, or if the drug causes its reappearance after recovery, it may be concluded that the drug had caused an increase in the local myocardial anoxia, presumably by vasoconstriction.* The following experiments were designed to ascertain the effects of digitalis upon the RS-T segment deviation after coronary ligation, before and during induced anoxemia.

METHOD

Sixty-three male or nonpregnant female cats, weighing at least 2.5 kg. each, were used in two series of experiments. In Series A, comprising seventeen cats,

the left branch of the left anterior descending coronary artery was ligated according to the technique already described.²⁴ On each of nine cats observations were made one week before operation, immediately after operation, and weekly for two or three weeks after operation. On eight cats observations were made only immediately after operation. All observations were made with the animals under light sodium pentobarbital anesthesia (30 mg. per kilogram, intraperitoneally), which has been shown to have no influence on the level of the RS-T segment of the electrocardiogram.²³ Standard three-lead electrocardiograms were made on each animal before and during the fifteen-minute administration of an atmosphere of 10 per cent oxygen. After the period of anoxemia, at least fifteen minutes of air breathing were allowed, and then crystalline ouabain* (0.25 mg. per cubic centimeter) was injected intramuscularly (0.1 mg. per kilogram). Thirty and forty-five minutes after the ouabain, electrocardiograms were made. One week after operation, electrocardiograms were made on seven of the first nine cats after the intramuscular administration of pitressin (1 unit per kilogram).

In Series B there were forty-six cats. Twenty-three were subjected to coronary ligation, and ten were controls which were not operated on. Twenty minutes after the coronary ligation, a continuous intravenous infusion of ouabain in saline at the rate of 1 c.c. per minute was started. The dilution of the ouabain was so adjusted for each cat that 3.3 micrograms per kilogram were administered per minute (0.1 mg. per kilogram would thus be administered in thirty minutes). The moment of cardiac standstill was recorded as the end point of this experiment.

Travell, et al.,²⁶ stated that in the cat with partially healed cardiac infarction (three weeks after operation), the fatal dose of digitalis is about 25 per cent less than for the normal cat, or for a cat immediately after operation. Because of this statement we subjected thirteen cats to coronary ligation, but did not give the ouabain solution until a week after the ligation. Each of the last five of these cats was infused simultaneously with two other cats; one was a control which had not been operated upon, and another had just been operated upon. Each of these five groups of three cats thus formed a unit, each member of which served as a control for the others.

RESULTS

Series A—Seventeen cats.—

1. Preligation electrocardiographic studies were done on nine cats. During the anoxemia two of these developed deviation of the RS-T segment. The average (sum of the deviations in 3 leads) for the nine cats was 0.2 mm. Complete return to the original state occurred when the cats were allowed to breathe air. The intramuscular administration of ouabain caused an RS-T segment deviation which averaged 0.4 mm. in six of the nine cats. After ouabain, anoxemia decreased the RS-T segment deviation in two of the six cats; the average was now only 0.3 mm.

Coronary ligation was deferred until one week after these control studies to allow sufficient time for elimination of the ouabain. Immediately after the operation eight of the cats showed RS-T segment deviation; the average for the nine cats was 3.2 mm. Anoxemia increased the RS-T segment deviation to an average of 4.0 mm., and all nine cats now showed changes. Upon recovery from the anoxemia and after the intramuscular administration of ouabain, the average RS-T segment de-

*Ouabain, Arnaud.

viation in eight cats was 4.3 mm. In the ninth cat there appeared a continuous run of ventricular premature beats, so that the RS-T deviation could not be studied. While under the influence of ouabain and during anoxemia, six of the cats showed an average RS-T segment deviation of 5.3 mm. One of the other cats developed right bundle branch block, with premature beats. A second showed a reversal of the direction of the RS-T segment deviation in all 3 leads, from a total elevation of 5.0 mm. to a depression of 2.5 mm.

In an effort to ascertain whether any of the observed ouabain effects were caused by central vagus action, atropine was given intravenously. There resulted an insignificant decrease in the total RS-T deviation.

The entire procedure, as described above, was repeated on the six surviving cats two or three weeks after the ligation and one or two weeks after pitressin, as described below. All six cats showed RS-T segment deviation which averaged 1.8 mm. During anoxemia this rose to an average of 2.2 mm.; three cats showed an increase and two a decrease. After the intramuscular administration of ouabain, all six cats showed increased RS-T segment deviation, which now averaged 3.4 mm. Anoxemia reduced the average deviation slightly (to 3.3 mm.); three cats showed a decrease, one an increase, and two no change.

The Effects of Pitressin: One week after the ligation, the RS-T segment deviation averaged 2.5 mm. in seven of the nine surviving cats; one of the seven showed no deviation. During induced anoxemia the average was 2.9 mm. Upon recovery from the anoxemia, pitressin (1 unit per kilogram) was injected intramuscularly. The pitressin increased the average RS-T segment deviation to 4.0 mm., and all seven cats were affected. During the course of the pitressin action, induced anoxemia resulted in a fall in the average RS-T deviation to 2.8 mm. in six cats; the seventh died after developing ventricular extrasystoles.

2. In the 8 cats upon which no preoperative observations had been made, there was an initial, average, postligation RS-T segment deviation of 1.5 mm. During anoxemia, the deviation increased to 1.8 mm. After the intramuscular administration of ouabain the deviation averaged 1.0 mm. in seven cats; the eighth developed a continuous run of extrasystoles. During the period of ouabain activity anoxemia increased the average RS-T segment deviation to 2.5 mm. in the seven cats; the aforementioned eighth cat continued to have the extrasystoles.

These results of the studies of the complete Group A are represented graphically in Fig. 1.

Series B—Forty-six cats.—

In this experiment the animals were subjected to a continuous infusion of ouabain in saline until cardiac standstill occurred. In twenty-three of the animals the infusion was started immediately after coronary artery ligation. In thirteen cats infusion was withheld until a week after the

ligation. The ten control animals were not subjected to coronary artery ligation, although pericardiotomy had been carried out in some.

The above experiments were performed in two groups. The initial group contained thirty-one cats. The animals with ligated coronary arteries died sooner after the start of the infusion than did the controls. There seemed to be little difference between the cats which were infused immediately after the operation and those which were infused one week after operation. In order to minimize the accidental distribution of these results, it was decided to run an additional series of fifteen cats in five parallel groups of three animals each: one, a control; one cat immediately after the ligation; and one cat which had been operated upon one week earlier. The results in this group agreed with those in the first group, so that the two groups are combined in a single report.

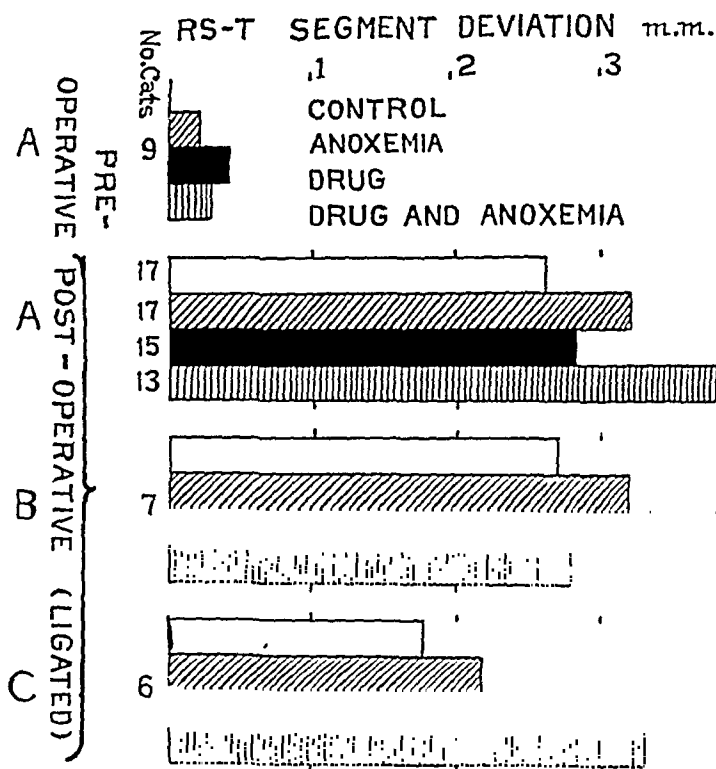


Fig. 1.—The effect of ouabain and pitressin on the RS-T segment of the electrocardiograms of cats (average), before and during induced anoxemia after experimental ligation.

A. Ouabain was given before and immediately after the ligation.

B. Pitressin was given one week after the ligation and the first dose of ouabain.

C. Ouabain was given two to three weeks after the pitressin injections at B.

In the ten control animals death occurred at an average of 60 minutes (35 to 72) after the start of the infusion. In the twenty-three cats which were infused immediately after the ligation, death occurred at an average of 50 minutes (37 to 62) after the start of the infusion, and in the thirteen cats which were infused one week after operation, death occurred at an average of 55 minutes (30 to 75) after the start

of the infusion. Thus, the ligation resulted in an increase of 16.7 per cent in sensitivity to ouabain in the cats which were studied immediately after operation, and in an increase of but 8.3 per cent when they were tested a week after operation. The scatter of the values for each group is such as to render insignificant the differences in the average of the three groups of cats. The over-all average of the forty-six cats was 53.6 minutes.

DISCUSSION

In the first group of experiments ouabain caused an increase in the deviation of the RS-T segment of the electrocardiogram after coronary artery ligation, although it did not do so in the normal cat. Similar results were obtained when pitressin was used one week after coronary ligation. It is reasonable to infer that the increase in the RS-T segment deviation from both ouabain and pitressin was due to the same cause, i.e., an increase in the myocardial anoxia produced by coronary artery constriction.

The RS-T segment deviation caused by the ligation was increased by the institution of anoxemia, which confirms our previous observations.²⁴ It corroborates the thesis that the RS-T segment deviation which follows ligation is a reflection of local myocardial anoxia, and can be exaggerated by induced anoxemia or by vasoconstrictors, such as pitressin. Since ouabain increased the RS-T segment deviation after ligation, and since this increase was further augmented by induced anoxemia, we have come to the conclusion that, after coronary ligation, ouabain causes coronary vasoconstriction.

Contrary to expectation, anoxemia resulted in a diminution of the large RS-T segment deviation which followed the administration of pitressin. It is assumed that the electrocardiographic changes which occur after the ligation of a coronary artery result from impaired oxygenation of that part of the myocardium normally supplied by the ligated vessel. The degree of local myocardial anoxia may be increased by the administration of a coronary constrictor, such as pitressin, or by the induction of generalized anoxemia by the administration of an atmosphere of 10 per cent oxygen. However, during generalized anoxemia of the type induced in these experiments, there are a rise in blood pressure of central origin, and an increase in the heart rate which is mediated through the sympathetic division of the autonomic nervous system.²⁷ The sympathetic supply to the coronaries is vasodilator, so that, other things being equal, anoxemia would increase the blood flow through the coronary arteries. The induction of anoxemia after pitressin may actually bring about an increase in flow through the coronary vessels, both by raising the blood pressure and by reflexly diminishing coronary arterial tonus, thus relieving somewhat the local myocardial anoxia. It is not suggested that the induction of anoxemia is necessarily a beneficial procedure, for the apparent electrocardio-

graphic improvement occurred only after severe embarrassment of the central nervous system by the anoxemia. Actually, the RS-T segment deviation in the cats with ligated arteries is more elevated by pitressin and anoxemia than by anoxemia alone.

Liebow and Feil²² studied the electrocardiograms of digitalized patients during exercise. They concluded that the electrocardiographic changes which they observed during exercise resulted from a diminished oxygen supply to the heart. In this case it is probable that the vasoconstrictor effects of digitalis exaggerated the myocardial anoxia of exercise, giving results which are similar to those obtained by us in cats.

Study of our second group of animals showed that cats which are treated immediately after coronary ligation are 17 per cent more sensitive to the lethal effects of ouabain than similarly treated controls which were either unoperated upon or had been subjected to pericardiotomy without ligation. Travell, et al.,²⁶ found no difference in susceptibility in their animals. These authors also found that cats were more susceptible to the digitalis bodies three weeks after coronary ligation than immediately after ligation. In our experiments, no great difference was observed between the two groups of animals. In fact, the cats which were infused with ouabain one week after ligation withstood larger doses of ouabain than those which were infused immediately after operation. The difference in the minimal lethal dose of ouabain between the controls and the cats with ligated arteries was not sufficiently great to warrant the conclusion that digitalis therapy is contraindicated after coronary occlusion in man.

SUMMARY

1. Ouabain was administered to seventeen cats before, immediately after, and two to three weeks after, coronary ligation.
2. The ouabain further increased the RS-T segment deviation which was induced by the ligation.
3. Pitressin, administered one week after coronary ligation, resulted in an exaggeration of the RS-T segment deviation.
4. Anoxemia, induced after coronary ligation, increased the RS-T segment deviation resulting from the ouabain, but decreased that produced by pitressin.
5. The minimal lethal dose of ouabain was less in cats with experimental coronary occlusion than in the controls, but increased somewhat when a week was allowed to elapse after the operation.
6. From the experiments detailed above, it is concluded that the digitalis bodies cause constriction of the coronary arteries of the cat. However, the constriction is not sufficiently great to increase significantly the toxicity of ouabain in cats with ligated arteries.
7. Our results do not indicate that digitalis is an especially dangerous drug to use after coronary occlusion in man.

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STUDIES ON CORONARY OCCLUSION

IV. VASODILATORS AND THE CORONARY CIRCULATION EXPERIMENTAL OBSERVATIONS

ALAN LESLIE, M.D., AND MICHAEL G. MULINOS, M.D.
NEW YORK, N. Y.

IN THE preceding paper¹ we reported that, after coronary artery ligation in the cat, digitalis and pitressin increased the RS-T segment deviation of the electrocardiogram both before and during induced anoxemia. This was interpreted to indicate that digitalis, like pitressin, constricted the coronary arteries. As a consequence of these observations, the effect of several so-called coronary dilators was investigated, using as the criterion of action the changes in the RS-T segment before and during anoxemia. These criteria are similar to those employed clinically,² and show promise of being useful as an approach to the problem of the pharmacodynamics of the impaired coronary circulation.

In cases of human coronary insufficiency, Levy and his collaborators,³ using the electrocardiographic effect of induced anoxemia as an index of coronary blood flow, reported that various drugs increased coronary circulation. Other investigators,⁴⁻¹¹ who employed a variety of methods of observation in animals, reported conflicting results from the use of the "coronary dilators." Coronary perfusion experiments and experiments on isolated segments of coronary arteries yield results which are not comparable directly to those which are obtained on intact animals.

The heart with an experimentally induced infarct may be considered as benefited by a given drug if the average size of the infarct is less than in untreated animals. This did not prove to be the case in a series of cats treated with papaverine,¹² and in another series reported by Gold, et al.,¹³ who used aminophylline. In both series the cardiac infarcts of the treated animals were of greater average size than those of the untreated controls. Fowler, Hurevitz, and Smith¹⁴ performed similar experiments on dogs, and found that the infarcts of the dogs treated with aminophylline were smaller than those of the untreated controls. It is suggested that these results were fortuitous, and that no conclusion should be drawn from data obtained by this method.

The present report deals with experiments which we believe to be less open to objection than those recounted above. By means of induced anoxemia after experimental cardiac infarction, a study was made of the effect of nitroglycerine, papaverine hydrochloride, and aminophylline upon the RS-T segment deviation of the electrocardiogram. The efficacy of the drugs was to be judged by the amount by which they reduced the

From the Department of Pharmacology, College of Physicians and Surgeons, Columbia University.

Received for publication April 22, 1942.

RS-T segment deviation caused by coronary ligation, under usual conditions as well as during induced anoxemia.

METHOD

Under sodium pentobarbital anesthesia the left branch of the left anterior descending artery was ligated in each of 16 cats, according to the technique previously described.^{14a, 14b} The cats were males or females, and weighed at least 2.5 kilograms each. The influence of each of the three drugs was observed immediately after the operation and at weekly or biweekly intervals thereafter. All observations were made with the animals under light pentobarbital anesthesia (30 mg. per kilogram), which has been shown to have no influence on the RS-T segment.¹² A fifteen-minute period of anoxemia (10 per cent oxygen) was followed by a recovery period of at least fifteen minutes of air breathing. The drugs were administered intraperitoneally because of the ease of injection; in order to reduce to a minimum any effects on blood pressure (discussed later), such as might occur after an intravenous injection of vasodilators; and in order to obtain more prolonged drug action than is usual after intravenous administration.

Electrocardiograms were made before and ten minutes after the administration of nitroglycerine, and again near the end of fifteen minutes of anoxemia. Another fifteen-minute recovery period brought the time to forty minutes after the administration of the nitroglycerine; this period was deemed ample for the full development of the action of the drug. Papaverine hydrochloride was then injected. In order to ascertain whether there were mixed drug effects, 8 sets of observations were made with papaverine, but without the previous administration of nitroglycerine. The injection of aminophylline was made forty-eight hours later in order to avoid an additive effect with the papaverine.

Forty-three sets of observations were made on the 16 cats. The dosages were varied over a wide range, as indicated in the following schedule.

1. Nitroglycerine—0.1, 0.25, 0.5, 1.0 mg. per kilogram.
2. Papaverine hydrochloride—3.0, 5.0, 10.0 mg. per kilogram.
3. Aminophylline—5.0, 10.0, 15.0 mg. per kilogram.

Blood pressure studies were made in the usual manner.

RESULTS

1. *Preoperative Observations* (16 cats).—

a. *Control*.—In 5 cats the total RS-T segment deviation was 3.0 mm. The average deviation for the 16 cats was 0.2 mm. During induced anoxemia the total deviation was 1.5 mm.; changes in the electrocardiograms of 2 cats accounted for the decrease. The average deviation was 0.1 mm.

b. *Nitroglycerine*.—The average RS-T segment deviation was 0.2 mm. During induced anoxemia the average increased to 0.3 mm.

c. *Papaverine Hydrochloride*.—The average RS-T deviation was 0.2 mm., with an increase to 0.3 mm. during anoxemia. Since the papaverine was injected during the period of nitroglycerine action, these figures show no further increase as a result of the papaverine.

d. *Aminophylline*.—The average RS-T segment deviation was 0.2 mm., with a decrease to 0.1 mm. during anoxemia.

It is evident that the administration of these drugs before the ligation caused only minor changes in the RS-T segments of the electrocardiograms of 5 of the 16 cats. These 5 cats might have been discarded as hypersensitive. They were not discarded in order to avoid over-weighting the results in favor of the drugs, and also in order to stress the importance of performing control observations on animals intended for coronary ligation.

2. *Postoperative Observations.*—

Postoperative observations were made at intervals from immediately after, to eighty-five days after, the ligation. Characteristic effects were noted throughout the postoperative period.

a. *Control.*—Ligation caused the appearance of an RS-T segment deviation in 15 of the 16 cats which totalled 67.0 mm. in the 43 observations. The average deviation per observation was 1.6 mm. During induced anoxemia all of the 16 cats showed an RS-T segment deviation which totalled 96.0 mm., and an average deviation of 2.2 mm., or an increase of 37.5 per cent.

b. *Nitroglycerine.*—There were 35 observations. The average deviation was 2.1 mm., or 31 per cent higher than before the drug. After the induction of anoxemia this increased to 2.4 mm.

c. *Papaverine Hydrochloride.*—Forty-three observations were made. The average deviation was 1.9 mm. This deviation is to be compared with 2.1 mm. as a control, for the papaverine was administered after the nitroglycerine. Therefore, papaverine resulted in a 10 per cent depression of the RS-T segment. During anoxemia the deviation was increased to 2.1 mm., or 13 per cent less than in the control. This "beneficial" effect of papaverine is shown also in the 8 observations which were made without the previous administration of nitroglycerine. These observations were made from six to eighty-four days after operation. The control readings, with air, averaged 0.56 mm.; 4 cats showed no deviation. This increased to 1.5 mm. under the influence of anoxemia. After papaverine hydrochloride (3 mg. per kilogram), the average deviation was reduced to 0.5 mm. Anoxemia after papaverine gave an average deviation of 0.75 mm., or 50 per cent less than when anoxemia was induced without papaverine.

d. *Aminophylline.*—There were 42 observations. The average deviation was 1.6 mm., which was raised to 2.1 mm. by the induction of anoxemia. These figures compare well with those of the controls.

It is obvious from these results that nitroglycerine and aminophylline, when given in the doses stated, had an adverse effect, or no effect, upon the RS-T segment deviation of the electrocardiogram after coronary occlusion. Since these drugs are smooth muscle depressants, the opposite result was to be expected; therefore, the effect observed by us is not easy to explain. One possibility, which may apply especially to nitroglycerine, is that these drugs may lower the blood pressure

sufficiently to elicit central vasoconstricting effects, but the experiments detailed below show that none of the three drugs, as given by us, lowered blood pressure sufficiently.

Papaverine alone, or after nitroglycerine, lowered the RS-T response of anoxemia, which suggests that this drug does actually dilate the coronaries under the conditions of this experiment.

3. *The Effect of the Vasodilator Drugs Upon the Blood Pressure of the Cat.*—

Nitroglycerine, papaverine hydrochloride, and aminophylline, when injected intravenously, usually cause a fall in blood pressure. To test out the possibility that the surmised beneficial effect of these drugs on the electrocardiogram might have been masked by a fall in blood pressure, experiments were performed on 3 cats after coronary ligation. The drugs were given intraperitoneally and in conformity with the routine of the previous experiments. Over a fifteen-minute period, anoxemia caused a rise in blood pressure of 5 to 15 mm. Hg. Nitroglycerine (0.75 mg. per kilogram) did not affect the blood pressure. Papaverine hydrochloride (15 mg. per kilogram) and aminophylline (25 mg. per kilogram) caused a fall in the blood pressure of 10 to 15 mm. Hg. Such a fall in blood pressure did not elicit any changes in the RS-T segment.¹⁴ Anoxemia, induced during the slight depression of the blood pressure, caused an increase. It may therefore be concluded that the RS-T segment deviations observed after coronary ligation, and any further alteration by the three drugs, were not contributed to by changes in blood pressure induced by the drugs which we used.

DISCUSSION

The data obtained after experimental coronary ligation indicate that, of the three vasodilators, nitroglycerine increased, papaverine hydrochloride depressed, and aminophylline did not modify appreciably, the RS-T segment deviation of the electrocardiogram. The data also indicate that the "coronary vasodilator" effect of these drugs was not masked by a fall in blood pressure, for it was shown (a) that the fall in blood pressure was slight, and (b) that only a much greater fall in blood pressure modifies the RS-T segment.¹⁴

The lack of effect of aminophylline on the RS-T segment may be due to several causes. (a) The doses used by us may not have been sufficiently large. (b) In experimental coronary ligation of the type employed in these experiments, there is a chance that the collateral circulation is poor, and therefore the drugs may reach the anoxic vessels in insufficient amounts to be effective. We know that blood does reach the area of cardiac tissue involved in the ligation because induced anoxemia increases the RS-T segment deviation which was produced by the ligation.¹⁴ (c) A species difference may explain the beneficial effects obtained in man by Williams, et al.,² who used a number of xanthine

derivatives. (d) In man, the pathology of cardiac infarction after "coronary occlusion" differs materially from that of experimental ligation. The noninfarcted cardiac muscle which is still functioning is not normal. (e) It is believed that in the conscious animal, coronary occlusion is regularly accompanied by vasospasm,¹⁵ whereas, in experimental coronary ligation, as it is usually performed, there may be little or no associated vasospasm because of the surgical anesthesia. In fact, it is possible that, in the cat, there is dilation of the blood vessels collateral to the ligated area as a result of the anoxemia, and it may not be possible to increase further this dilation by the use of vasodilator drugs.

The "beneficial" effects of papaverine are in keeping with our previous observations,¹⁶ as well as of those of Linder and Katz,^{17, 18} who obtained obvious coronary vasodilation when the perfusion fluid contained papaverine hydrochloride in a concentration of 1:120 to 1:1190; these concentrations could not be attained in *in vivo* experiments. Our own experiments indicate that no such concentrations are necessary, for vasodilator effects were observed with the use of 3 mg. per kilogram intraperitoneally.

SUMMARY

1. Observations were made on the effect of nitroglycerine, papaverine hydrochloride,* and aminophylline upon the RS-T segments of the electrocardiograms of 16 cats under sodium pentobarbital anesthesia. The cats were studied (a) before and during induced anoxemia, and (b) before and at intervals after coronary ligation.

2. The three vasodilators lowered the blood pressure less than 15 mm. Hg, and only for a short time.

3. Lowering of the blood pressure artificially by acute withdrawal of blood had no effect upon the electrocardiogram until a blood pressure of about 30 mm. Hg was reached, when induced anoxemia resulted in a greater RS-T segment deviation than previously.¹⁴

4. The RS-T segment deviation produced by coronary artery ligation was increased by nitroglycerine; papaverine hydrochloride decreased it after the nitroglycerine, as well as when no previous medication had been given. Aminophylline had no consistent effect.

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Clinical Reports

CONGENITAL PULMONARY STENOSIS WITH CLOSED CARDIAC SEPTA

REPORT OF A CASE WITH COMMENTS REGARDING THE CIRCULATION TIME

ROGERS E. GARRISON, M.D., WISCONSIN RAPIDS, WIS., AND
ROBERT H. FELDT, M.D., MILWAUKEE, WIS.

INTRODUCTION

CONGENITAL stenosis of the pulmonary valve with closed cardiac septa is rare. In Maude Abbott's¹ collected series of 1000 cases of congenital heart disease, pulmonary stenosis with closed auricular and ventricular septa occurred nine times. The present case is reported because of the rarity of the lesion and because of the application of circulation time measurements to the diagnosis.

CASE REPORT

The patient, a 15-year-old eighth grade pupil, was seen first in March, 1940. She complained of increasing dyspnea and cyanosis of about one year's duration. She had never been cyanotic or dyspneic before. Careful questioning elicited no other complaints. Her birth was normal and she was not a "blue baby." At the age of five she became ill with fever and joint pains. These symptoms subsided in two or three weeks, but she was kept in bed for a year because her attending physician said she had rheumatic fever which affected her heart. For the next eight years she got along well by observing moderate restrictions in her physical activity because of "leakage of the heart." She was formerly well nourished, but in recent years she had become very thin. The father, mother, and two siblings were living and well.

In October, 1932, the patient visited the Mayo Clinic.* At that time there was no cyanosis. A systolic murmur and thrill were found in the pulmonic area. The roentgenogram of the chest was negative, and the electrocardiogram showed right axis deviation.

On examination the patient appeared poorly developed and poorly nourished. The lips, cheeks, conjunctivae, and mucous membranes were moderately cyanotic, and the fingers and toes were markedly cyanotic. There was clubbing of the fingers and toes. The extremities were cold. The pulse rate ranged from 96 to 116. The blood pressure could not be measured by the auscultatory method, but, by palpation, the systolic blood pressure was 88 to 93 in both arms. The only other abnormalities were those referable to the heart. The apex impulse was in the fifth intercostal space, 6.7 cm. from the midsternal line. There was a pronounced systolic thrill in the second and third left intercostal spaces. The first sound at the apex was loud, and at times it was split. A loud, low-pitched, blowing systolic murmur was heard

*We are indebted to Dr. R. J. L. Kennedy, of the Mayo Clinic Staff, for this information.

Received for publication May 13, 1941.

over the whole precordium and posteriorly in the left interscapular space. The point of maximum intensity of the murmur was in the second left intercostal space, just to the left of the sternum. The pulmonary second sound was diminished.

Fluoroscopic examination showed a normally active heart of normal size. There was marked prominence of the pulmonary conus as viewed in the anteroposterior and right anterior oblique positions. A roentgenogram confirmed the fact that the pulmonary conus was prominent.

The erythrocyte count was 8,100,000 per cubic millimeter, and the hemoglobin was 19.6 Gm. per 100 c.c. The arm-to-tongue circulation time, measured with 10 per cent calcium levulinate, was 10 seconds. When 20 per cent calcium gluconate was used, the circulation time was 11 seconds. Both readings were considered to be within normal limits.

A diagnosis of congenital stenosis of the pulmonary artery, with interventricular septal defect, was made. Activity within the limit of the patient's ability was recommended.



Fig. 1.—The markedly hypertrophied right ventricle is shown above the left ventricle in this photograph of the heart in tranverse section.

The patient continued in school and remained fairly well until December, 1940, when the dyspnea and cyanosis became more intense. When she was seen March 5, 1941, she had mild grippe. The dyspnea was somewhat greater than formerly, but the other features were unchanged. She made a rapid recovery from the acute infection. On March 10, 1941, the patient experienced two attacks of severe dyspnea and died in the second attack. A few hours before death the pulse rate was 112. There were no rales in the lungs and there was no edema of the extremities.

POST-MORTEM EXAMINATION

Only a limited autopsy was permitted. The pericardium was normal. The heart was not weighed, but it appeared to be normal in size. The apex was formed by the right ventricle. The auricles were not dilated or hypertrophied. The average thickness of the right ventricular wall was 28 mm. (Fig. 1). The wall of the left

ventricle averaged 21.5 mm. in thickness. The capacity of the right ventricular cavity was estimated at 10 c.c. The cardiac septa were closed. The cusps of the pulmonary valve were fused into a cone, at the apex of which there was an opening 2 mm. in diameter (Fig. 2). At the anterior commissure there was a slit, 3 mm. in length, which did not connect with the above-mentioned opening. The valve surface about the opening was surrounded by a 3 mm. band of pinkish, moderately friable vegetations. The pulmonary artery appeared slightly decreased in diameter, and its wall was smooth. The aortic valve and the aorta were normal. The mitral valve was thickened and slightly deformed by firm, fibrous nodules. There was no fusion of the cusps. The chordae tendineae were thickened and shortened. There were fresh vegetations on the line of closure of the valve. The tricuspid valve was similarly deformed, but to a less extent; there were a few fresh vegetations at the line of closure. The lungs were crepitant and the sectioned surface was dry.



Fig. 2.—The pulmonary artery is laid open to show the slit-like opening in the pulmonary valve which is surrounded by an areola of vegetations. The prosector's middle finger is in the dilated pulmonary conus.

COMMENT

In the presence of pulmonary stenosis with a septal defect there is usually a shunt of venous blood from the right side of the heart into the arterial blood of the left side of the heart. In such cases the circulation time from the arm to the tongue is greatly shortened. The stimulating drug does not have to go through the pulmonary circulation before it reaches the tongue, so that it gets to the tongue much more quickly. McGuire and Goldman² have reported circulation times of four seconds in cases of congenital heart disease with venous-arterial shunt. They found that the average circulation time for normal children was 10.6 seconds.

In the present case, the circulation time was normal. This factor alone should have led us to consider a diagnosis of pulmonary stenosis with closed septa. The rarity of pulmonary stenosis without a septal defect caused us to diagnose the more common condition in spite of the normal

circulation time. The fact that the circulation time was normal and that closed septa were found at autopsy suggests that measurement of the circulation time may be a valuable adjunct to the differential diagnosis of septal defects with venous-arterial shunt.

The old rheumatic deformities of the auriculoventricular valves were incidental abnormalities. Since there was no auricular dilation or hypertrophy, the valve lesions must have produced little or no functional disturbance. The acute vegetations on the pulmonary and auriculoventricular valves may have been manifestations of bacterial endocarditis. There were no clinical signs of this disease.

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THREE CASES OF LOCALIZED GUMMATOUS MYOCARDITIS

DAVID M. SPAIN, M.D., AND MAX W. JOHANNSEN, M.D.
NEW YORK, N. Y.

IN THE laboratory of pathology at Bellevue Hospital, in the past year, we have encountered three examples of gummata of the heart; in one of the cases there was, in addition, extensive gummatous pulmonary arteritis. Only seventeen cases of the latter disease are to be found in the literature.

There are two distinct types of myocardial syphilis, excluding the acute syphilitic myocarditis described by Warthin, about the existence of which there is a great deal of doubt, namely, diffuse and localized gummatous myocarditis.

CASE REPORTS

CASE 1.—A 63-year-old white railroad worker was admitted to the Fourth Medical Division, August 9, 1940, with the complaint of progressive swelling of the abdomen for three months. For the preceding ten years he had been treated for arteriosclerotic heart disease. However, he had had no symptoms of diminished cardiac reserve until about two years before admission, when he noted some breathlessness on climbing stairs. Three months before admission he first noted swelling of the abdomen. Two months later, edema of the ankles was first noted. For ten days prior to admission his dyspnea increased markedly.

Upon admission the patient was markedly cyanotic and dyspneic, and the cervical and abdominal veins were engorged. The blood pressure was 90/70. The apex impulse of the heart was in the fourth left intercostal space outside the mid-clavicular line. The sounds were poor in quality, and the heart rate was 108. The pulmonic second sound was louder than the aortic second. There were a coarse systolic murmur at the apex and a harsh systolic murmur over the pulmonic area. Fluid was present in the abdomen.

The blood Wassermann reaction was strongly positive. An electrocardiogram revealed auricular fibrillation, coupling, and intraventricular block.

The patient grew worse rapidly, and died suddenly on the sixth day.

Necropsy Observations.—Necropsy was performed twenty-four hours after death. The abdomen was distended and contained 1500 c.c. of clear yellow fluid. The lower extremities were very edematous.

The pericardial sac was completely obliterated by fibrous adhesions. The heart weighed 900 grams and, in situ, presented anteriorly only the greatly enlarged right ventricle. On opening the right ventricle, we found a large, yellow, nodular mass which replaced and apparently invaded the columnae carneae and papillary muscles, and extended into the pulmonary conus, immobilizing the pulmonary leaflets and stenosing the valve. The pulmonary artery itself, for a distance of about 6 cm. from its origin, presented similar, small, scattered nodules (Fig. 1). The tricuspid leaflets were normal, but their chordae tendineae were shortened by invasion by the gummata of the corresponding papillary muscles. On section, this tissue had a bacon-like appearance. The left auricle and ventricle were moderately hypertrophied, but showed no dilatation. The mitral and aortic valves showed minimal calcification. There was no separation of the commissures of the aortic

From the Laboratories of Pathology, Bellevue Hospital.
Received for publication June 14, 1941.

valve. The coronary ostia and arteries were patent throughout. The aorta showed slight atherosclerosis.

Microscopic examination revealed that the yellow nodules consisted, at their periphery, of myocardium which was pale and poorly preserved, with moderate fibrosis and small round cell infiltration, especially in the perivascular areas. More central to this, there was a well-demarcated and unusually well-vascularized area of necrotic myocardial fibrosis, through which were scattered numerous lymphocytes, plasma cells, and occasionally multinucleated giant cells of the Langhans type.



Fig. 1.—The heart in Case 1, showing massive gummatous involvement of right ventricle and pulmonary artery.

This zone blended into a dark brown, completely necrotic mass in which no cellular structure was recognizable (Fig. 2). Levaditi's stain for spirochetes and special stains for tubercle bacilli showed nothing. Sections through the yellow nodules in the pulmonary artery revealed essentially the same histologic picture. Sections through the intervening areas revealed perivascular lymphocytic and plasma cell infiltration and vascularization of the media. The latter was indistinguishable from syphilitic mesaortitis.

Microscopic examination substantiated the gross diagnosis of massive gummatous involvement of the right ventricular myocardium and gummatous pulmonary arteritis.

CASE 2.—A 56-year-old, white woman, formerly a showgirl, was admitted October 7, 1940, to another hospital, and transferred to Bellevue Hospital three days later. The transfer summary stated that the patient had shown the signs and symptoms of congestive heart failure for one month prior to admission. Because the patient developed a psychosis, she was transferred to the Third (New York University) Psychiatric Division, Bellevue Hospital.

The previous history presented nothing worthy of note in the present connection.

The patient appeared much younger than she actually was. She was cyanotic but not dyspneic. The lower extremities were very edematous from the ankles to the knees. The liver was palpable 3 cm. below the costal margin.

The heart was enlarged. The rhythm was normal, and there were occasional premature contractions. The rate was 52 per minute, and the blood pressure, 100/60. A systolic murmur was heard over the apex and base. A superficial neurologic examination showed nothing abnormal. Psychiatric examination confirmed the diagnosis of psychosis of a type not definitely determined.

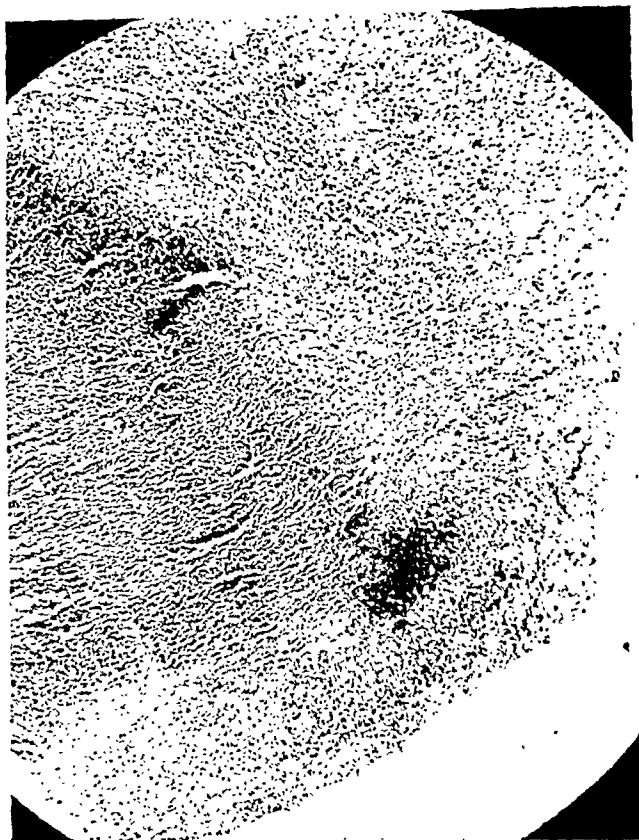


Fig. 2.—Photomicrograph of section through gumma in Case 1—H. & E., paraffin; $\times 100$.

The electrocardiogram showed low voltage, with auriculoventricular dissociation. The blood Wassermann reaction on admission (reported after death) was strongly positive. A roentgenogram of the chest was reported as showing cardiac enlargement in all diameters, with accentuation of all cardiac curves and obliteration of the cardiovascular angle. The other laboratory data were negligible.

The course was characterized by progressive failure and increase in stupor. The patient was treated with diuretics, sedatives, and oxygen. Thirty-six hours after admission she died; this was approximately five weeks after the onset of signs and symptoms of cardiac failure.

Necropsy Observations.—Necropsy was performed twenty-six hours after death. The lower extremities and subcutaneous tissues of the abdomen and chest were edematous.

The heart weighed 500 grams. The right auricular appendage contained an organized thrombus. The apex of the right ventricle adjacent to the interventricular

septum was thinned and very hemorrhagic. An organizing thrombus was attached to the endocardium in this area.

The left auricular endocardium was studded with small, smooth, rounded, firm nodules. On section they were yellowish-white and extended into the auricular wall (Fig. 3). The posterior mitral leaflet measured over 1 cm. in thickness, thus stenosing the mitral orifice. Its auricular surface presented a nodule similar to those in the auricle. It extended into the center of the leaflet, where a grayish-red

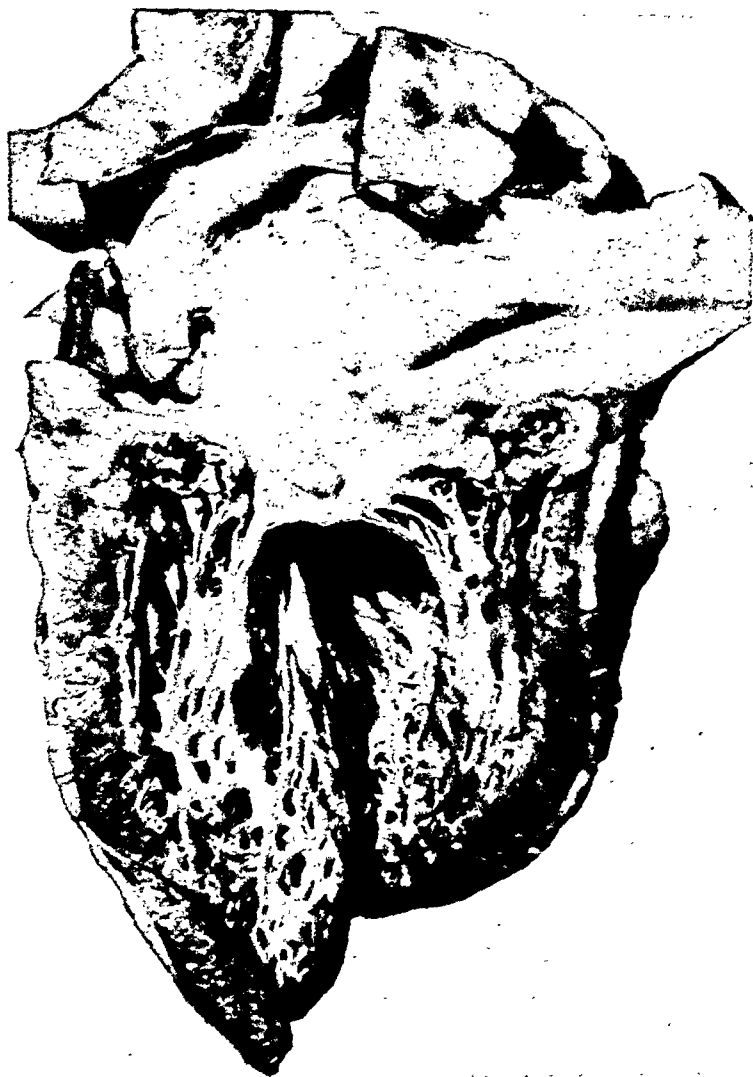


Fig. 3.—Heart in Case 2, showing multiple gummata of the left auricular wall, with involvement of posterior mitral leaflet.

necrotic mass was found, which, in turn, gradually merged with a grayish-white nodule in the left ventricular myocardium. The anterior mitral leaflet, the aortic cusps, and the coronary arteries were normal. The left ventricular myocardium revealed many small areas of fibrosis, but no nodules other than those already described.

The aorta contained numerous yellow and pearly-white plaques with wrinkling.

Microscopic examination revealed that the various nodules in the heart consisted of a central area of necrosis which gradually changed into loose connective tissue, slightly infiltrated by both large and small round cells, plasma cells, and macrophages (Fig. 4). The aorta showed thickening and fibrosis of the adventitia,

with lymphocytic and plasma cell infiltration and perivascular cuffing. The media exhibited numerous scars and vascularization, with round cell infiltration. Levaditi's stain and acid-fast stains failed to reveal either spirochetes or tubercle bacilli.

Microscopic examination substantiated the gross diagnosis of multiple gummata of the myocardium, endocardium, and mitral leaflet, and syphilitic aortitis.

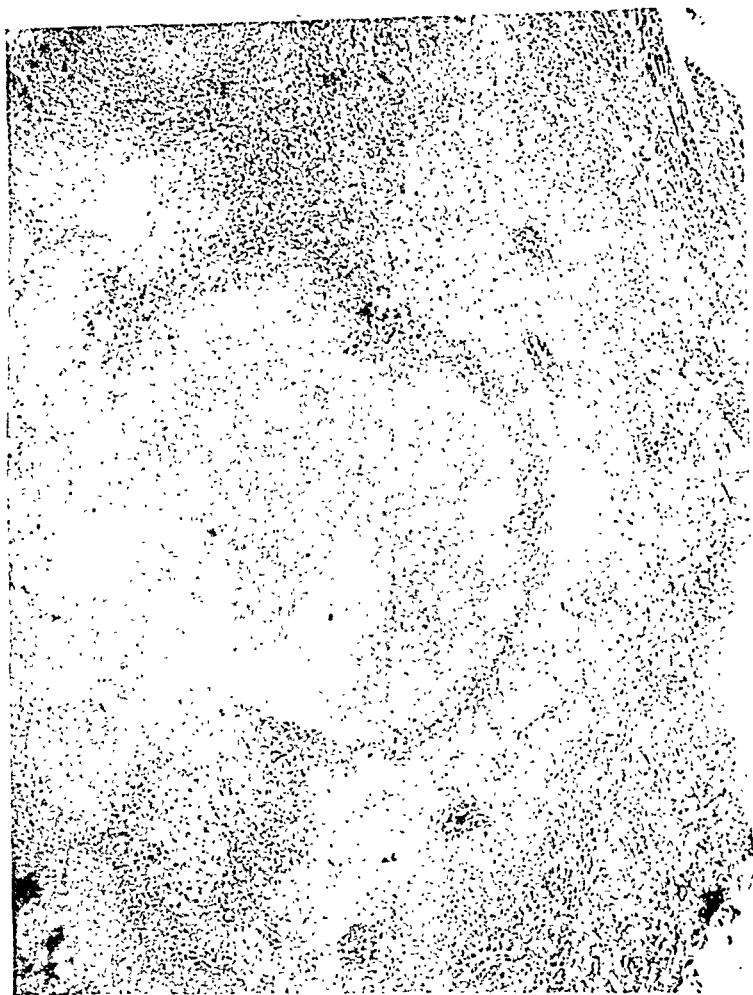


Fig. 4.—Photomicrograph through one of the gummata in Case 2. H. & E., paraffin: $\times 100$.

CASE 3.—A 53-year-old Greek waiter was admitted November 14, 1940, to the Third (New York University) Medical Division of Bellevue Hospital. Ten weeks before admission, the patient suddenly collapsed while walking and was unconscious for a few minutes. Similar attacks recurred twice, and, because of the frequent occurrence of dizzy spells, the patient entered another hospital. There the cardiac lesion was thought to be myocardial fibrosis, resulting in partial intraventricular heart block. The patient had had a chancre in 1922, and was treated with six injections. After the blood Wassermann reaction was found to be strongly positive, the patient was treated with intramuscular injections. Otherwise, treatment was symptomatic. After discharge from that hospital, the attacks of dizziness and syncope reappeared, and the patient was finally admitted to Bellevue Hospital.

Physical examination revealed a blood pressure of 150/62 and irregularity of the heartbeat, with a ventricular rate of 58 and a pulse rate of 42. The size of the heart was at the upper limit of normal. A systolic murmur was heard at the

apex. The second aortic sound was accentuated. The sounds were of good quality. The liver was palpable 5 cm. below the costal margin; it was smooth and not tender. The testes were enlarged to four times their normal size. They were regular in outline and very firm. The patient had moderate edema of the ankles. The leucocyte count was 10,000, and the differential count was normal. The electrocardiogram showed complete auriculoventricular block, with idioventricular rhythm.

Shortly after admission, the patient lost consciousness for fifteen seconds, ceased to breathe, and no heart sounds were audible. Gradually, cardiac contractions were resumed and the patient recovered. Thirty-six hours after admission the patient died.

A clinical diagnosis of myocardial gumma was made.



Fig. 5.—Heart in Case 3, showing a gumma in the interventricular septum.

Necropsy Observations.—Necropsy was performed forty-eight hours after death. Except for evidence of congestive heart failure, the relevant pathologic changes were confined to the cardiovascular system and to the right testicle.

The heart weighed 400 grams. The left ventricle was only slightly enlarged. The coronary arteries were sclerotic and their lumina narrowed. In the interventricular septum, near the base, there was an area about $1\frac{1}{2}$ cm. in diameter which was pale yellow, in contrast to the smooth, glistening, white endocardium elsewhere. On section this lesion was found to consist of yellow-white, homogeneous, and soft but nonfriable tissue, only fairly well circumscribed, which faded gradually into normal myocardium (Fig. 5). This lesion extended through the entire thickness of the interventricular septum, sparing only the endocardium of the right ventricle. There were two other similar lesions adjacent to this one in the upper-

most part of the interventricular septum. The combined lesions involved both the membranous and muscular portions of the interventricular septum. Elsewhere the myocardium appeared normal.

The aorta showed a moderate degree of wrinkling and pearly-white elevations. The right testis was only indistinctly outlined and was surrounded by a mass of grumous, yellowish material.

Microscopic examination of the myocardial lesion showed a much thickened endocardium overlying fairly well-vascularized, loose, collagenous tissue, with some amorphous debris which resembled caseous material. The surrounding area, especially about blood vessels, was infiltrated with plasma cells, lymphocytes, and a few polymorphonuclear leucocytes. Many young connective tissue cells, with large pale nuclei, were seen (Fig. 6). The aorta showed scarring and vascularization of the media. The swelling of the right testis was identified as a gumma.

Microscopic examination confirmed the gross diagnosis of gumma of the myocardium, syphilitic aortitis, and gumma of the right testicle.

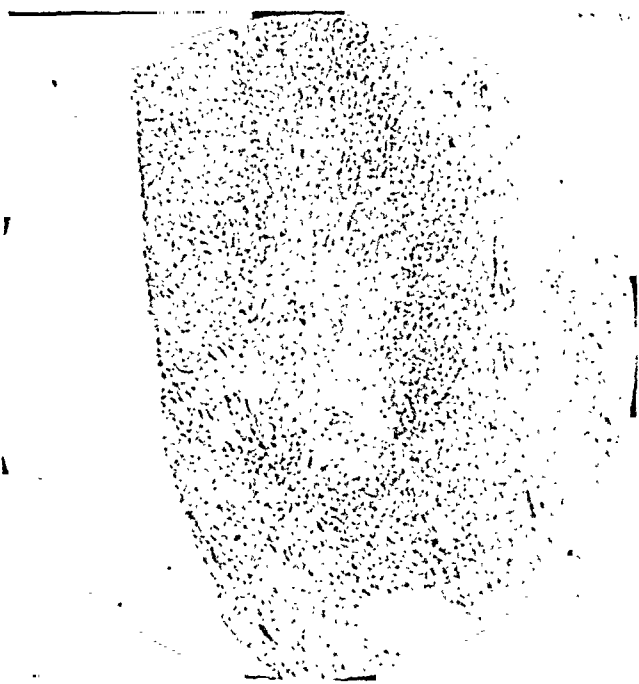


Fig. 6.—Photomicrograph of section of gumma in Case 3; H. & E., paraffin; $\times 100$.

COMMENT AND SUMMARY

Three cases of localized gummatous myocarditis are reported. The electrocardiograms in all three cases revealed conduction defects. In Case 1, the gumma impinged on both the tricuspid and pulmonary valve leaflets, producing functional impairment. In Case 2, the gummatous tissue invaded the posterior mitral leaflet and produced stenosis and insufficiency. None of the three patients presented enough clinical signs for the diagnosis of any of the commoner cardiac disorders.

Although stains for spirochetes were negative, each of the three hearts presented gross and microscopic lesions characteristic of syphilis elsewhere than in the myocardium. In addition, the blood Wassermann reaction in all three cases was strongly positive.

ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH ACUTE PORPHYRIA

MAURICE ELLASER, JR., M.D., AND BENJAMIN O. KONDO, M.D.
SAN FRANCISCO, CALIF.

THE vascular changes which occur in acute porphyria have been mentioned by several authors.¹⁻⁴ Hypertension and renal disease have been observed so frequently in this condition that they are considered an integral part of the syndrome, together with psychic instability,⁵ abdominal phenomena which usually simulate mechanical ileus, neurologic changes of the flaccid paralytic variety, and porphyrin in the urine. A slight tendency toward photosensitivity may or may not be present. Waldenström^{1, 5} stated that the renal disease and hypertension in acute porphyria are caused by arteriospasm. He described a case in which he detected angiospasm of the retinal arteries in the presence of amaurosis. In previously reported cases, sufficient coronary arterial spasm to produce anginal pain has not been noted either clinically or electrocardiographically.

The patient with whom we are here concerned had hypertension, as well as the usual neurologic, psychic, and abdominal symptoms that are associated with a severe acute attack of porphyria. There was no clinical evidence of cardiac disturbance that could be classified as congestive failure, or that suggested coronary arterial disease. The electrocardiographic changes during the acute attack and the return to normal as the condition subsided may well represent evidence that the associated coronary artery spasm was neither permanent nor the direct result of the action of that particular form of porphyrin which was detected in the urine in this case. This conclusion is supported by the observation that, in spite of the remarkable clinical improvement, relatively large quantities of the porphyrin which was present during the exacerbation were still found in the urine. Waldenström⁵ stated that the porphyrin which is excreted in the urine is not necessarily the substance that causes the neurologic changes. It may well be that this porphyrin likewise is not the substance which causes the vasospastic phenomena.

CASE REPORT

M. R., a white, married housewife, aged 32 years, entered the San Francisco Hospital January 11, 1939.

Chief Complaint.—Abdominal pain of two days' duration.

Present Illness.—The patient had been in the hospital on several occasions between April and December, 1938, and diagnoses of chronic alcoholism, partial bowel

From the Department of Medicine, University of California Medical School, and the Laguna Honda Home Infirmary, Department of Public Health, San Francisco.

Presented before the Pacific Interurban Clinical Club, San Francisco, February 21, 1941.

Received for publication June 10, 1941.

obstruction, and right ureteral stricture had been made. In December, 1938, she had been discharged after a two-day attack of fever, associated with "intestinal obstruction" of unknown etiology. Low abdominal pain, pain in the back, and anorexia had persisted.

Two days before entry on January 11, 1939, she had an attack of nausea and vomiting during which she expelled clear, mucoid material. Subsequently, sharp, cramp-like, generalized abdominal pain became evident. These symptoms persisted, with short respites. On the following day the pain radiated to the hips and the vomitus became bile-tinged.

Family History.—The family history was negative in regard to any illnesses that might have been manifestations of porphyria.

Past History.—The patient stated that sedatives, possibly of the barbitol group, had been given to her for insomnia and nervousness during a period of emotional and psychic instability before the neurologic changes had developed. In 1938, a hysterectomy had been performed. An injury sustained in childhood had resulted in blindness of the right eye.

Physical Examination.—The patient was a well-developed, well-nourished woman. At the time of examination she was obviously in great pain. The head and skin were normal. Anisocoria was present. The left pupil gave normal responses to light and in accommodation. The right eye showed evidences of exophoria and was blind. The nose, mouth, neck, thorax, and breasts were normal. The heart was normal except for a soft, basal systolic murmur. The peripheral vessels were palpably normal. The pressure in the brachial artery was 176/116. The pressure was equal in the two arms. The abdomen was flat and symmetrical, with a low mid-line scar; tenderness was elicited in all quadrants to deep palpation. There was no evidence of guarding, rebound phenomenon, or ascites. Borborygmi were normal. The muscular development of the extremities was normal and no wasting was noted. Normal reflexes were obtained bilaterally. Sensation to touch was slightly diminished below the knees. The psychiatrist who examined the patient suggested that the recurrent, unexplained, abdominal pain might be caused by psychic trauma, and that the patient might be addicted to narcotics.

Laboratory Examination.—Urine analysis on January 12, 1939, disclosed a clear amber color; a pH of 5.5; a specific gravity of 1.024; a slight trace of albumin; no reducing substances; a few hyaline casts; and 3 erythrocytes to each high dry field. The hemoglobin value was 84 per cent on the Saldi scale, with 4,470,000 erythrocytes per cubic millimeter. There were 6,800 leucocytes per cubic millimeter, 71 per cent of which were neutrophils and 8 per cent eosinophilic polymorphonuclear cells. The blood Wassermann reaction was negative. The radiologic report was as follows: "There is a minimal gaseous dilatation of the colon, no evidence of intestinal obstruction or opaque calculi." Excretion pyelograms showed "poor filling of the left kidney probably due to spasm but no evidence of pathologic findings in the genitourinary tract." The skull also was normal radiologically.

Course.—On January 30, 1939, the patient complained of inability to use her hands, arms, and legs. Neurologically, her condition was said to resemble astasia abasia. Lumbar puncture revealed no abnormalities of either pressure relationships or chemical content of the spinal fluid. The urine for the first time was of a reddish-amber color, and the hemoglobin had dropped to 59 per cent (Saldi).

Two days later the patient was transferred to the psychiatric service. A central type of facial palsy, vertical nystagmus, a generalized flaccid paralysis of the extremities, and a decreased response to faradic stimulation were noted. The sensations were normal. Laryngeal paralysis, muscular pain, and hyperesthesia subsequently developed. Trichinosis and periarteritis nodosa were suspected, but biopsy of the pectoral muscle was negative for both encysted trichinae and arterial changes. The precipitin test for trichinosis was negative also. The fasting blood urea nitrogen was 47 mg. per cent. The electrocardiogram is presented in Fig. 1.

Four months later, on May 9, 1939, the patient was transferred to the Laguna Honda Home Infirmary. Her physical and mental status was but slightly changed. Later it was evident that atrophy of the muscles of the hands, legs, and arms was becoming progressively more severe. Left lateral nystagmus was demonstrated. The deep tendon reflexes were absent. No sensory changes had occurred. In October, 1939, dysphagia, with nasopharyngeal regurgitation of food, and dysarthria occurred. Subsequently, evidences of aspiration pneumonia were noted. It was at this time that the diagnosis of acute porphyria was made and proved by spectroscopic identification of porphyrin in the urine. Therapy was instituted with calcium and vitamins (including vitamins A, B, C, D, and G, but excluding vitamin

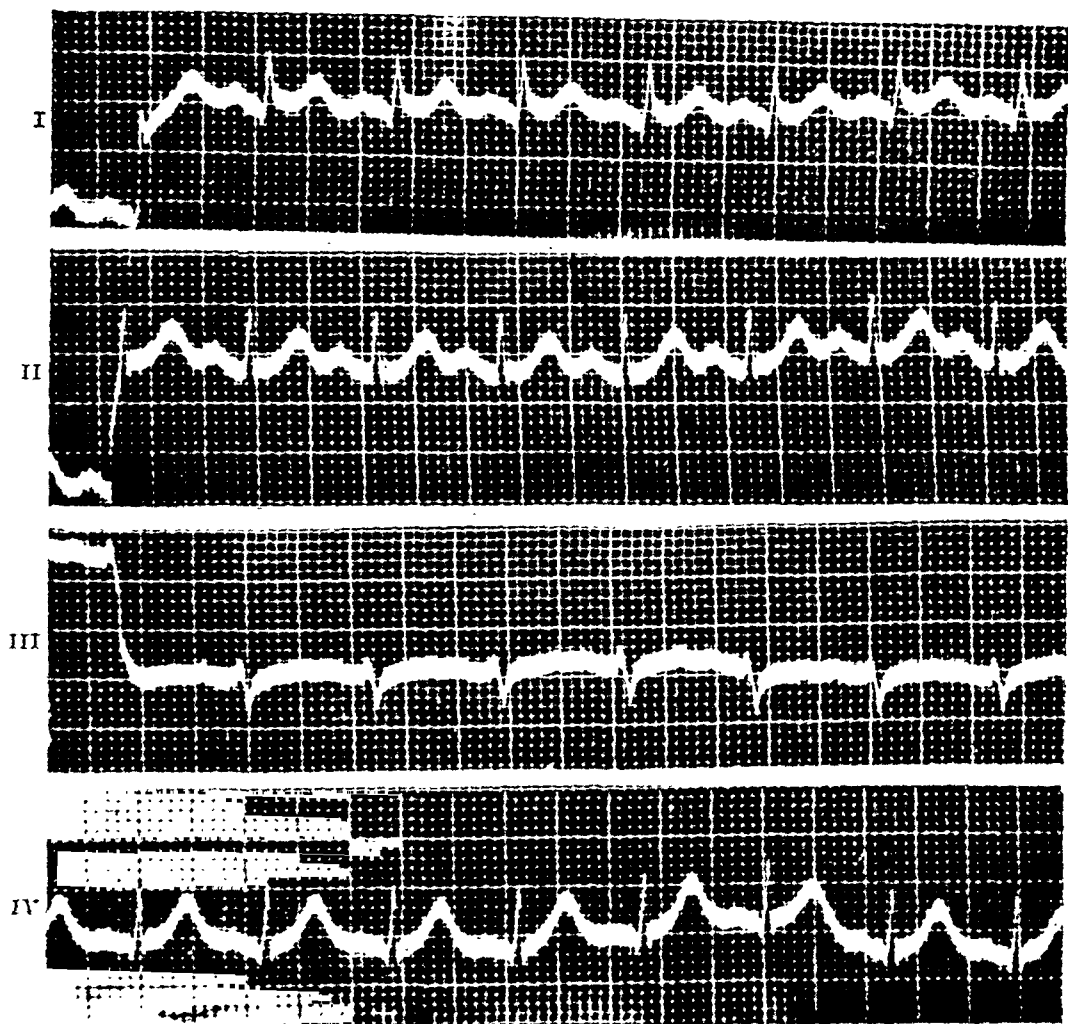


Fig. 1.—Electrocardiogram recorded February 25, 1939. The patient manifested the neurologic changes noted in the case report, as well as hypertension and renal disease. Apparent are sinus tachycardia, marked elevation of the S-T segment in Lead I, diminished voltage of the major deflections, and left axis deviation. Lead IV is the IV-F of the Committee on Precordial Leads of the American Heart Association.

E) in large doses (especially the vitamin B complex). Iron and liver extracts were administered both orally and parenterally. As no improvement had occurred on this regime after four months, the administration of alpha tocopherol was begun April 26, 1940, and all other medication was discontinued. The results are noted in Fig. 2. This form of therapy has been continued to the present time. The patient is continuing to improve. Her motor power has increased so that she can walk unsupported. Her mental aberration no longer exists; she is remarkably

stable emotionally, and has acute insight, especially in regard to the periods of alcoholism and psychic instability which were prominent at the onset of the illness. Wrist and ankle drop of moderate degree persist. Bulbar disease is not evident. All deep tendon reflexes are obtainable. No reaction of degeneration can be dem-

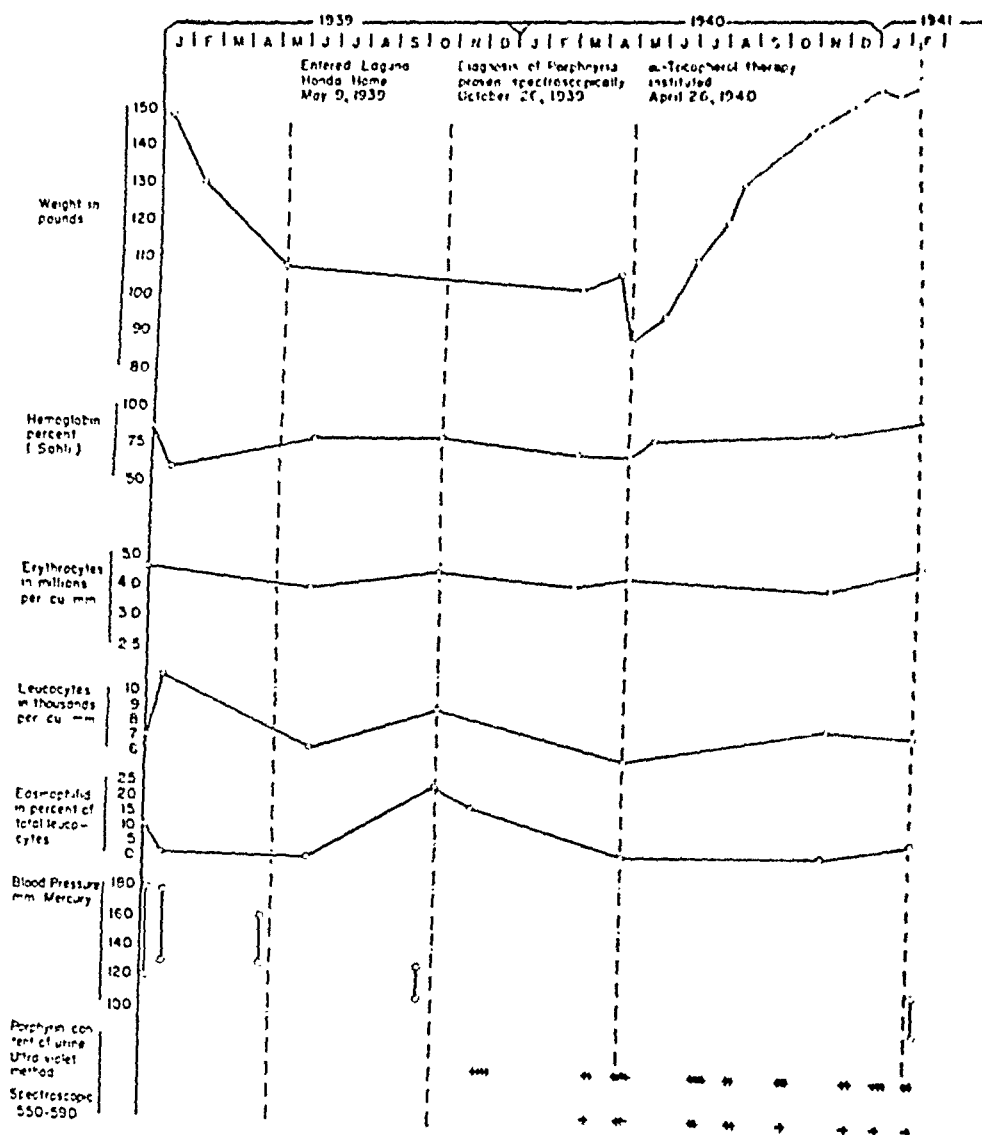


Fig. 2.—Graphic representation of the clinical course in a case of acute porphyria, showing the remission which occurred coincidental with the administration of alpha-tocopherol.

onstrated. Her weight is 152 pounds; the hemoglobin and erythrocyte count are normal; the blood pressure is 122/76. The porphyrin content of the urine is shown in Fig. 2. An electrocardiogram taken June 28, 1940, two months after she began to improve, is shown in Fig. 3, and another, taken February 24, 1941, is shown in Fig. 4.

DISCUSSION

The electrocardiographic abnormalities at the onset of the exacerbation were in all probability the result of coronary arterial spasm, and

strongly suggest that the acute attack was associated with transient anterior coronary artery disease. Judging from the reports of others who have recorded electrocardiographic changes in acute hypertensive states,⁶ we conclude that hypertension alone could probably not produce such changes. The abnormalities in the electrocardiogram consist principally of elevation of the S-T segment in Lead I and slurring of the S-T segment in Lead III. Elevation of the S-T segment in Lead I is certainly not the usual result of uncomplicated hypertension.

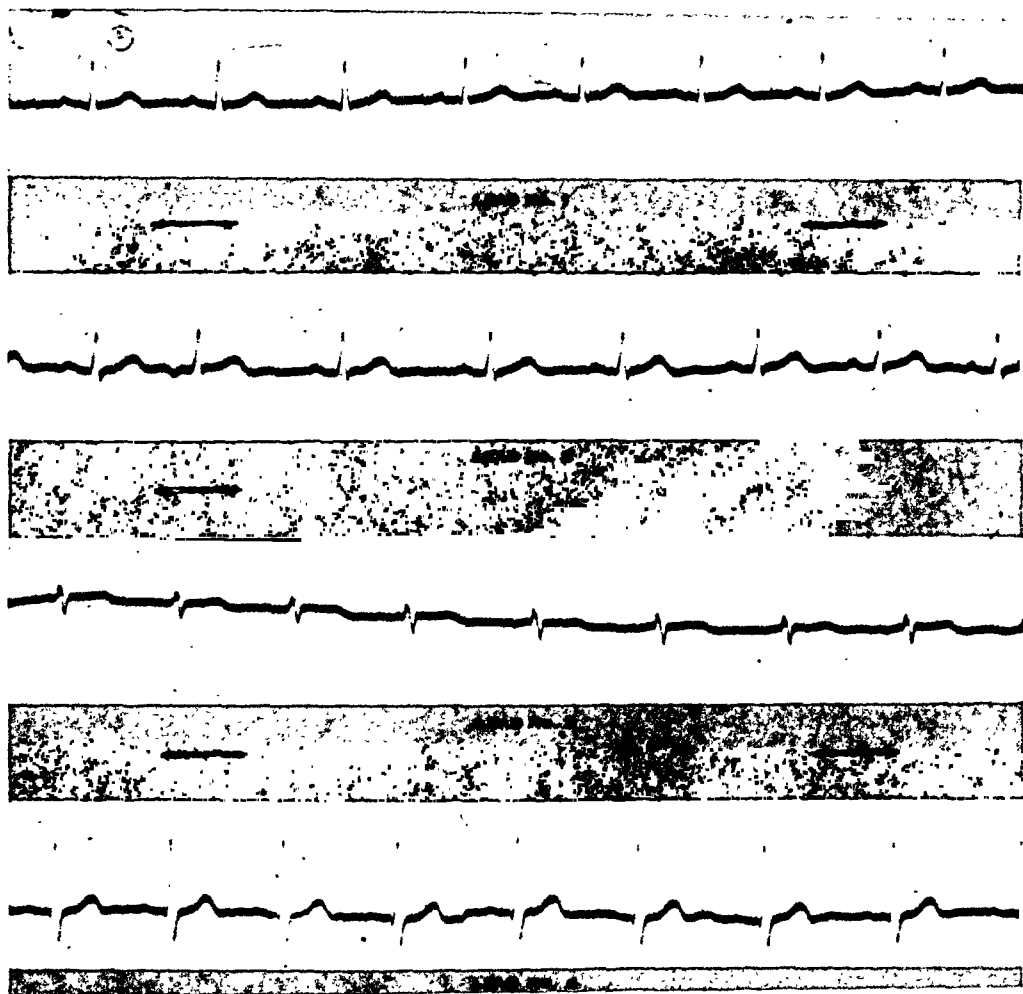


Fig. 3.—Electrocardiogram recorded June 28, 1940, during the period of remission, without hypertension or evidence of renal disease. The rate is 80 per minute, the S-T segment in Lead I is normal, and the voltage of the major deflections is increased.

Whether the hypertension in acute porphyria is the result of renal ischemia, peripheral vasomotor changes, or both, has not yet been ascertained. The electrocardiographic changes are apparently caused by transient myocardial ischemia, rather than actual cardiac infarction. They are evidently the result of coronary arterial spasm, which is but one aspect of the general phenomenon of angiospasm—probably the fundamental physiologic derangement in acute porphyria.

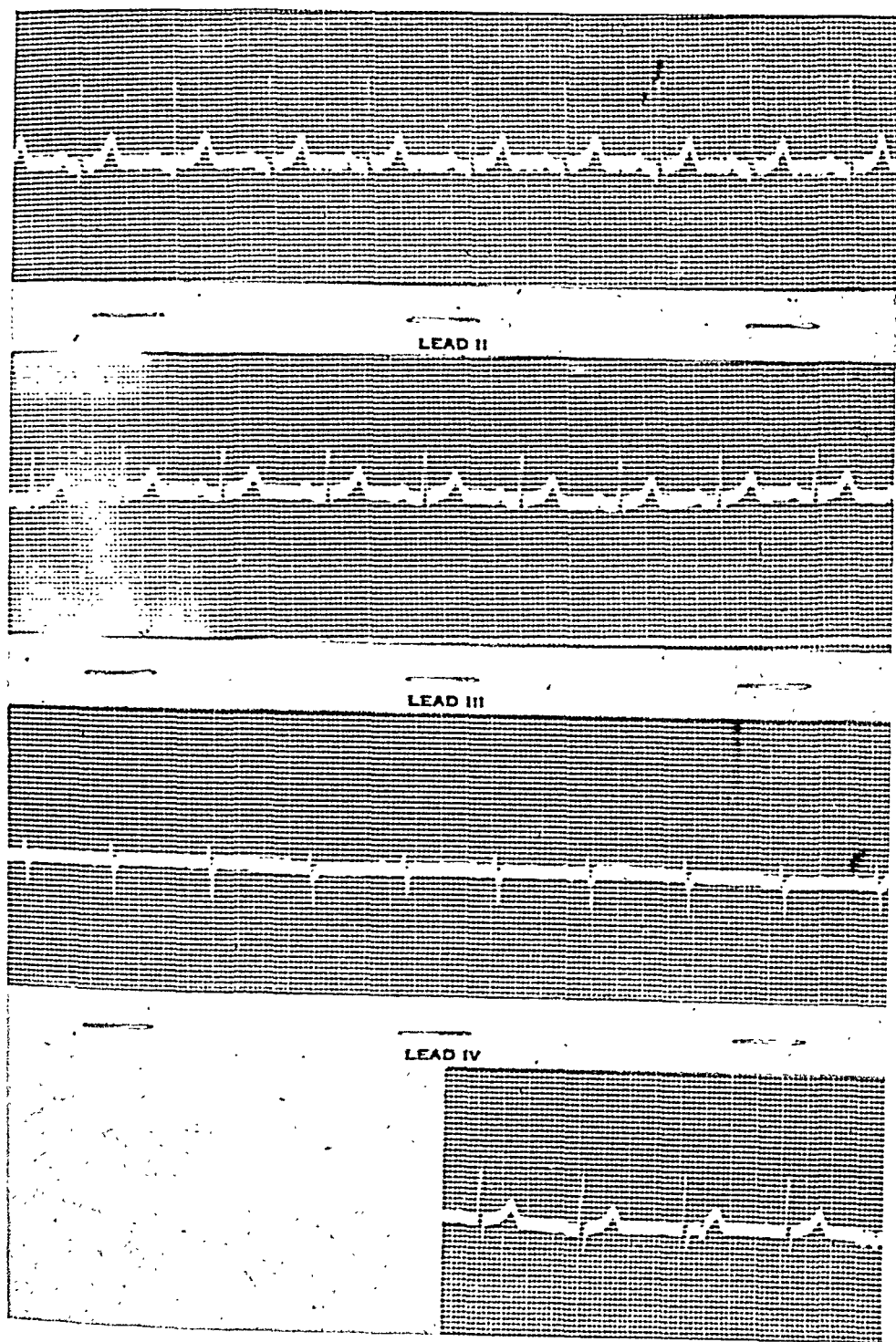


Fig. 4.—Electrocardiogram taken February 24, 1941, during the period of continued improvement. The axis deviation remains to the left, the voltage has increased to normal, and the S-T segments have returned to normal.

SUMMARY

The clinical report of a patient who was observed in an exacerbation and remission of acute porphyria is presented.

The electrocardiographic changes that occurred suggest that the angio-spasm which is known to be an outstanding phenomenon in this disease involves the coronary arteries as well as other blood vessels.

The reversion of the electrocardiogram to normal with the subsidence of the syndrome was sufficiently well defined to warrant the conclusion that the vasospasm is of a transient nature and does not produce permanent myocardial disease.

We are grateful to Dr. Gordon E. Hein for his guidance and for the spectroscopic determinations of porphyrin in connection with this case.

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TRAUMATIC RUPTURE OF THE RIGHT VENTRICLE AN UNUSUAL CASE

WILLIAM STEIN, M.D., AND EUGENE REVITCH, M.D.
NEW BRUNSWICK, NEW JERSEY

IN 1935, Claude S. Beek¹ reviewed the subject of contusions of the heart and outlined the following mechanisms by which rupture of a heart takes place as a result of nonpenetrating forms of trauma to the chest.

1. Contusion of the heart, with subsequent softening. This softening is usually greatest during the second week, and there is the possibility of cardiac rupture at that time.

2. Increasing intracardiac pressure by the application of compression force to the legs or abdomen.

3. Broken ribs driven into the heart.

4. Bursting the heart by compression between sternum and vertebrae.

In the same year, Bright and Beek² completely reviewed 152 cases of cardiac rupture in the literature up to that time, and cited only one in which rupture was caused by compression of the heart between the sternum and spine; this would fall into Group 4, as outlined above. Review of the literature since then shows no similar case.

CASE REPORT

S. E., a well-nourished and well-developed white boy (age, 12 years; height, 5 feet 2 inches; weight, 145 pounds), had always been well except for measles. There was no history of rheumatic fever, syphilis, or congenital cardiac anomaly.

On February 1, 1941, he was riding on a sled, face down. The sled was tied to the rear of an automobile and was being pulled at a slow speed for the pleasure of the boy. A companion jumped directly on him to share the ride. He flung himself lengthwise on the boy as children often do. The latter let out a peculiar noise that alarmed the lad on top of him, and he, in turn, called on the driver of the car to stop. When they looked at the victim he was quiet and nonresponsive. They immediately rushed him to the hospital, where the intern (one of us, E. R.) pronounced him dead.

Autopsy was performed by Dr. William C. Wilentz. External examination revealed the following significant points. The body was flaccid and cold. The lips were cyanotic. There was a 3 inch by 1 inch brush abrasion contusion mark over the right anterior portion of the chest wall at the level of the nipple and to the right of the sternum. There was no further evidence of external injury or violence. Internal examination revealed no evidence of any fracture of the ribs, but slight hemorrhage was present in the intercostal tissues directly underneath the external contusion abrasion. The right lung was normal. The left lung was normal in size, but the lowermost part of the lower lobe was severely contused, and, on section, showed much hemorrhage. The pericardial sac was tremendously distended

Department of Medicine, Middlesex General Hospital, New Brunswick, N. J.
Received for publication June 26, 1941.

with free and clotted blood. The right ventricle was ruptured throughout its entire length (Fig. 1). The heart was otherwise normal. The liver, spleen, and kidneys were normal in size and appearance, but showed mild congestion. The remaining viscera and cavities were normal.

It was evident that the child had died immediately of cardiac tamponade caused by rupture of the right ventricle.



Fig. 1.—Traumatic rupture of the right ventricle.

COMMENT

Bright and Beck,² Hawkes,³ and Barber^{4, 5} call attention particularly to the fact that living cardiac muscle is very susceptible to rupture by abnormal external forces. No one part of the heart is injured more than any other, when all of the reported cases are considered.

The cause of the death of this child was no doubt the same as in most other cases. The compressive force was probably applied to the chest when the cardiac cycle was at the end of diastole or beginning of systole, when the heart was filled with blood. If, in addition, the glottis happened to be closed and the chest was in the inspiratory phase, conditions for transmission of the compressive force from the chest to the heart would be particularly favorable.

It seems to us that the right ventricle ruptured in this particular instance because its wall is thinner than that of the left ventricle.

SUMMARY

A case of complete rupture of the right ventricle, resulting in hemo-pericardium, cardiac tamponade, and immediate death, is reported. The rupture was caused by the application of a sudden compressive force to the chest.

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Abstracts and Reviews

Selected Abstracts

Schroeder, H. A.: Arterial Hypertension in Rats. I. Methods. *J. Exper. Med.* 75: 513, 1942.

Normal standards for the blood pressure of rats under pentobarbital sodium anesthesia have been ascertained. Arterial hypertension did not consistently follow the injection of estradiol and pitressin in adult rats, and only transient hypertension occurred after the injection of dihydroxyphenylalanine. The injection of adrenalin in oil, however, was followed by cardiac hypertrophy, and it also resulted from (a) partial constriction of one renal artery, (b) the production of unilateral hydro-nephrosis, (c) traumatic injury to one kidney, (d) inducing unilateral perinephritis with a cellophane membrane. The blood pressure in many of the animals became elevated.

In rats the weight of the heart is probably a more reliable index of the presence of the hypertensive state than is one measurement, or two, of blood pressure under anesthesia. The latter is extremely variable, both in normal and in hypertensive animals. Rats are, however, liable to hypertension under natural circumstances, and it can be easily induced in a number of ways. The weight of the heart may then become rapidly increased. To judge from the findings in this species, rats are very susceptible to the production of the hypertensive state, in comparison with other animals.

AUTHOR.

Wolferth, C. C., Livezey, M. M., and Wood, F. C.: Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms. *Am. J. M. Sc.* 203: 641, 1942.

Electrocardiograms made between small areas situated along a line drawn from the C_1 position to the tip of the right acromion (the right arm being regarded as an electrically intermediate position between the tip of the acromion and the axilla) all show a ventricular contour similar to Lead CR_1 , provided the same polarity is used in all these leads as in CR_1 . This we have called the C_1 pattern of potential. The size of the deflections seems to be related to the potential variations at the C_1 position; the distance of the paired areas from the heart; and their distance from each other.

Electrocardiograms made between small areas situated along a line drawn from a position slightly outside the cardiac apex to the tip of the left acromion (the left arm being regarded as an electrically intermediate position between the tip of the acromion and the axilla) all show a ventricular contour similar to that of the CL lead made to the position just outside the cardiac apex, provided the same polarity is used in all these leads as in the CL lead. This we have called the C_2 pattern, although it may be derived from the C_4 or C_6 position, depending on the relation of the cardiac apex to the chest wall. The size of the deflections seems to be related to the potential variations at the C_2 position; the distance of the paired areas from the heart; and their distance from each other.

By pairing appropriate areas along each of these two lines and making electrocardiograms with the same polarity as in Lead I, a series of tracings closely resembling Lead I can be obtained. The deflections become larger as the paired areas approach the C_1 and C_6 positions.

Various combinations of three positions can be found along each of these two lines whose relationships are such that the ventricular potential of the intermediate position is approximately equal at all instants to the mean of the ventricular potentials of the proximal and distal positions.

The above-mentioned findings suggest that there is marked decrement in the C_1 pattern between the C_1 position and the right shoulder and also marked decrement in the " C_6 pattern" between the position just outside the cardiac apex and the left shoulder. However, there appears to be very little alteration in contour of either pattern along these radial lines from the precordium to shoulder tip.

By methods described in the text, combinations of three positions can be found along each of the two lines, whose relationships are such that the sum of the ventricular potential of the area nearest to the heart along one line plus that of the two areas farther from the heart on the other line is approximately equal at all instants to the sum of the potentials of the other three areas. Furthermore, when such positions have been found, the relationships of the three areas on each side are such that the potential of the proximal area minus the sum of the potentials of the two distal areas on one side is approximately equal at all instants to the potential of the proximal area minus the sum of the potentials of the two distal areas on the other side.

On the basis of the above-mentioned relationships, the following may be demonstrated:

1. Lead I can be reproduced by the application of electrodes to various combinations of four chest positions without electrodes on either arm.

2. Either the C_1 pattern of potential is almost completely responsible for the potential variations of the right arm and the " C_6 pattern" of potential is almost completely responsible for the potential variations of the left arm, or else there is an additional pattern of potential variation common to all these areas which is not reflected in the tracings because it is identical at areas so near the heart as the C_1 and C_6 positions, and so far away as the right arm or tip of the right shoulder and the left arm or the tip of the left shoulder.

3. No matter which of the above alternatives is correct, Lead I represents the subtraction of the C_1 pattern of potential variation after it has undergone decrement, from the " C_6 pattern" after it has also undergone decrement.

4. If the first alternative stated above in "B" is correct, a method can be devised for recording the potential variations of the ventricular origin in a single area. If the second alternative is correct, the method as described records the potential variations of a single area minus the hypothetical concealed pattern of potential common to all the areas mentioned in "B." Thus, no matter which alternative is correct, the study of potential patterns can be simplified by the elimination of the obscuring effects of the C_1 and " C_6 patterns" present in upper parts of the body.

The presence of the C_1 and " C_6 patterns" of potential can be demonstrated below the diaphragm by appropriate methods. No test was made for other anterior chest patterns. The rather scanty evidence now available, however, indicates that a pattern or patterns of potential which seem to exert comparatively feeble effects above the diaphragm (at least in the formation of the C_1 and C_6 patterns) influence greatly either the potential variation of the lower part of the body or the hypothetical concealed potential not subject to the decrement in the upper part of the body. From the practical point of view it would appear to make little difference which of these alternatives is correct.

Limited studies of the lower esophageal pattern of potential (below the level at which the electrode is in close contact with auricular muscle) suggest that the part of the heart responsible for this pattern has a marked effect on the form of the ventricular electrocardiogram when an area above the diaphragm (at some distance from the precordium) is paired with an area below the diaphragm.

The pattern of esophageal potential, at and above the level where the electrode is in close proximity to auricular muscle, resembles that which has been described as the endocardial pattern of potential variation more closely than it resembles the epicardial pattern. The effects of this pattern are probably not entirely negligible on the body surface.

The relationships among potential differences on the body surface resulting from cardiac electrical activity appear to be different from what Einthoven conceived them to be when he formulated the equilateral triangle hypothesis. The demonstration that certain patterns of potential variation found to exist in positions near the heart remain intact in positions far from the heart, except for decrement, and the relationships discovered as a result of these phenomena indicate the necessity for reconstructing electrocardiographic theory. An attempt has been made to begin this reconstruction.

AUTHORS.

Öhnell, v. R. F.: Concerning Paroxysmal Tachycardia: Two Families in Whom an Inclination to Heart Failure and Fixed Changes in the Electrocardiogram Were Constant. *Cardiologia* 5: 326, 1941.

Two families with disposition to heart attacks have been described (frequency-changes, sensorial symptoms in the heart region, almost unconsciousness, polyuria, etc.—these symptoms combined or single). In the electrocardiogram between attacks, there is often a gradual rise of the initial part of the QRS-complex. Other electrocardiographic changes are also described. The possibility that we are dealing here with one and the same hereditary disease has been discussed.

Apparently, paroxysmal tachycardia may be due to hereditary causes.

AUTHOR.

Perera, G. A., Levine, S. A., and Erlanger, H.: Prognosis of Right Bundle Branch Block: A Study of 104 Cases. *Brit. Heart J.* 4: 35, 1942.

An analysis of 104 cases of right bundle branch block has been prepared.

It was observed that reduplicated heart sounds, gallop rhythm, and pulsus alternans were uncommon in this series. The two latter disorders were noted in a small group that had advanced heart disease.

Forty per cent of the patients had no appreciable subjective discomfort from the heart. In fact, some have no subjective or objective evidence of heart disease apart from the right bundle branch block.

The average survival time after the diagnosis of right bundle branch block of 29 fatal cases, was three years. If the 6 cases that came into the hospital more or less moribund and died within a few days are excluded, the average survival period of the fatal group was four years and five months. Of the 62 patients alive when last seen or heard from, the average survival period was four years and one month. The longest survival period amongst the living cases was seventeen years, and amongst the fatal cases, sixteen years and seven months.

The clinical impression that patients with right bundle branch block have a distinctly more favorable prognosis than do those with a left bundle branch lesion has been sustained.

AUTHORS.

Campbell, M.: Inversion of T Waves After Long Paroxysms of Tachycardia. Brit. Heart J. 4: 49, 1942.

After long paroxysms of tachycardia the T waves may become inverted in one or more leads for some days. This does not indicate any organic disease, but is a completely reversible process indicating some degree of exhaustion or strain of the heart muscle.

AUTHOR.

Stein, W., and Uhr, J. S.: Congenital Heart Block: Report of a Case. Brit. Heart J. 4: 7, 1942.

Complete heart block represents an inability of the stimulating impulses originating in the sino-auricular node to pass through the auriculoventricular node and the main bundle of His, so that the auricles beat at their own rate while the ventricles contract at the rate governed by the auriculoventricular node that has taken over the function of pacemaker, which is usually 30 to 50 beats a minute, or if conduction from the latter is impaired also, then at their own ventricular rate, which is usually below 40 beats per minute. This heart block may be congenital, which is rare, or acquired, which is more usual.

Yater (1929) reviewed 30 cases of congenital heart block reported up to that time, and established certain criteria that would permit one to classify a case as being congenital. These were the following five points:

1. Electrocardiographic evidence of the block existing.
2. A slow pulse that had been found present at an early age and had continued to be present.
3. The absence of any history suggestive of an infection that might have produced the block, as diphtheria, congenital or early acquired syphilis, rheumatic fever, or chorea.
4. A history of any one of the following: syncopal attacks, fainting spells (explained on the basis of the Adams-Stokes syndrome), vertigo, headaches, nausea and vomiting after unusual exertion, convulsions, dyspnea, and/or cyanosis. (These findings may or may not be present and are not absolutely requisite for the criteria, but if present add further evidence.)
5. The presence of a congenital heart lesion, namely, patent interventricular septum (the latter at times being subject to an acquired endomyocarditis, quite infrequent in this instance as far as the septum itself is concerned).

While theoretically it might be possible to explain the heart block on a prenatal myocarditis or syphilis involving the bundle of His or a developmental defect affecting the bundle of His, these are most unlikely to occur for practical considerations.

This case fits the criteria of Yater (1929).

The etiology of congenital heart block is organic and is based on the pathological presence of a patent interventricular septum. Such septal defects, both large and small, are a common deformity and are found relatively frequently. Why they occur clinically without the presence of heart block so often, is odd, but has been explained correctly as follows: The usual site of the interventricular defect is anterior to the pars membranacea while the A-V bundle lies behind it (Leech, 1930). Inasmuch as the ventricular complexes in the electrocardiogram of complete heart block are normal, it follows that the lesion responsible for the block must be in the course of the main bundle of His, above the bifurcation close to the septum (Lampard, 1928).

The reason for the almost constant preservation of the muscular connection between the auricles and ventricles probably lies in the fact that the special bundle ap-

pears in the fifth week of fetal life, whereas the membranous separation between auricles and ventricles take form between seven and ten weeks. The bundle is preserved between the posterior endocardial cushion and the posterior portion of the annular fibrosis (Yater, Leaman, and Cornell, 1934; Moll, 1912; and Tandler, 1913).

It is only when the A-V node or main bundle of His is caught in the congenital anomalous development of the septum, or is caught in the excessive formation of fibrous tissue of the membranous portion of the septum interfering with the continuity of the bundle, that heart block occurs (Aitken, 1932).

The prognosis in general is guarded. A few cases have reached mature adult life. It must be remembered that a patent interventricular septum is associated often with other congenital cardiac anomalies, the most frequent being the tetralogy of Fallot. These anomalies are overshadowed by the dangers of an engrafted endocarditis. If the concomitant anomalies are small and do not limit the functional capacity of the heart permitting the subject to survive early life, there is no reason to consider the prognosis unfavorable, barring an unlooked-for bacterial endocarditis.

AUTHORS.

Van Bogaert, A., and Van Baarle, F.: Contribution to the Study of Arterial Hypertension in Connection With the Hypothalamo-Hypophyseal System. *Cardiologia* 5: 273, 1941.

Starting with the conclusions of a former paper dealing with the role of the hypothalamus in the genesis of a chronic arterial hypertonia, comparable to essential hypertonia in man, the authors have explored the eventual role of the hyperactivity of the hypophysis and the normal secretion of the hypophysis on exciting the hypothalamic centers and tracts. After a critical study of the biological signs of a hyperactivity of the hypophysis in the case of essential hypertonia, the authors come to the following conclusion: The freeing of the encephalobulbic sympathetic pressure centers determines on the one hand the arterial hypertonia and on the other a hypersecretion of the hormones of the hypophysis. Many animal experiments enabled the authors to prove this hypothesis. The presence of hypophysis hormone in larger quantities than the normal in the biological fluids in no way allows one to conceive a causal connection between the secretion of the hypophysis and the increase in the blood pressure, since both are the independent consequences of an excitation of the sympathetic encephalobulbic centers, amongst them that of the hypothalamus.

AUTHORS.

Marvin, H. M.: The Diagnosis of Coronary-Artery Disease. *New England J. Med.* 226: 251, 1942.

The clinical evidence that points to coronary arteriosclerosis consists of a clear history of anginal heart failure in the absence of the other infrequent causes, the occurrence of acute myocardial infarction, or the presence of congestive heart failure if other types of heart disease and vitamin deficiency can be excluded.

The roentgenologic evidence of coronary arteriosclerosis is present if calcification of the vessels can be demonstrated, if there is a ventricular aneurysm, or if localized reversal of ventricular pulsation is revealed by fluoroscopic examination.

If myocardial infarction is excluded, there is no change in the electrocardiogram that in itself justifies the diagnosis of coronary disease, because the alterations on which this diagnosis is based may be—and often are—due to other causes.

AUTHOR.

Lisa, J. R., Magiday, M., and Hart, J. F.: **Peripheral Arteriosclerosis in the Diabetic and Nondiabetic: A Study of One Hundred and Six Amputated Legs.** J. A. M. A. 118: 1353, 1942.

The peripheral vascular pathologic condition of 109 amputated legs was studied. There were 56 diabetic specimens and 53 nondiabetic specimens. The two types were in the same age period. The women outnumbered the men in the same diabetic group. The opposite was true in the nondiabetic group. The arterial changes were similar in the two groups. Acute venous occlusions and phlebosclerosis were more frequent among the nondiabetic. Infection with cellulitis was only slightly more frequent in the diabetic group. Dry gangrene occurred almost as frequently in the diabetic as in the nondiabetic. The occlusive element in arteriosclerosis is the dangerous feature in both types. The terms dry and wet gangrene do not properly describe the conditions found. More rigid criteria and more careful differentiation between the lesions secondary to occlusive arterial disease and those due to infection should be instituted.

AUTHORS.

Harkins, H. N., and Schug, R.: **The Surgical Management of Varicose Veins: Importance of Individualization in the Choice of Procedure.** Surgery 11: 402, 1942.

In a series of varicose vein operations personally conducted on 98 extremities of 63 patients during 1940, 217 incisions and 19 strippings were done.

A stereotyped operation should be avoided. The surgical procedure should be individualized to fit the patient and to block all important venous incompetencies as determined by complete diagnostic tests.

High ligation and segmental excision of the saphenous vein and all its branches at the fossa ovalis should be performed in all cases submitted to surgery.

Additional ligations and excisions lower down on the thigh or leg should be performed as indicated.

Stripping gives a better cosmetic result than excision and is preferable to the latter except in cases of superficial, friable, or recently sclerosed veins and for veins high in the thigh.

Injection as an adjunct to surgery is best postponed until the second week after operation.

Important points in the surgical technique include the use of local anesthetic, silk, transfixion of main vessels, elastoplast bandages, and ambulatory cure in all cases.

The one ill effect of consequence in these cases was a slight increase in the edema of one leg in two cases and a marked edema in another case.

AUTHORS.

Bosse, M. D., and Strang, J. M.: **Chronic Occlusion of Portal Vein: Report of Two Cases, One a Case of Occlusion Associated With Aneurysm of the Splenic Artery and Carcinoma of the Liver (Hepatoma).** Arch. Path. 33: 372, 1942.

Two cases of chronic occlusion of the portal vein by calcific thrombi are reported. One of the patients was a white man 58 years old. The occlusion was associated with aneurysm of the splenic artery and hepatoma of the liver. The portal thrombosis in this case was probably secondary to acute appendicitis. The thrombosis involved tributary and dilated collateral veins as well as the main portal stem. The other patient was a white man 38 years old. The occlusion may have resulted indirectly from mitral stenosis. Both patients had sclerosis of the portal system.

The aneurysm of the splenic artery was of the cirroid type. The hepatoma was associated with portal cirrhosis. Only one report of chronic portal occlusion associated with aneurysm of the splenic artery was found in the literature. Association of primary carcinoma of the liver with either chronic portal occlusion or aneurysm of the splenic artery was not found.

AUTHORS.

Altschule, M. D., Gilligan, D. R., and Zamcheck, N.: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man. IV. The Lung Volume and Pulmonary Dynamics. *J. Clin. Investigation* 21: 365, 1942.

Studies of the effect of the injection of fluids intravenously on the subdivisions of the lung volume and on the respiratory dynamics have been made in six normal subjects.

Injection intravenously of 1800 c.c. of isotonic sodium chloride solution, at rates of 39 to 185 c.c. per minute, in these normal subjects caused no change in residual air, and only slight decreases in the vital capacity, its components, the reserve and complemental airs, and in the total lung volume. The respiratory minute volume showed no consistent change, although the tidal air was usually decreased. All the changes in pulmonary function found after intravenous infusions in these normal subjects were insignificant.

The slight decreases in vital capacity, its components, and the total lung volume, after these massive intravenous infusions at rapid rates in these normal subjects, are interpreted as due to slight pulmonary vasodilatation associated with temporarily increased blood volume.

The fact that changes in pulmonary dynamics and lung volume, following rapid intravenous injections of large volumes of fluid in normal subjects, were at most only slight, in no way alters the clinical concept that when it is necessary to administer fluids intravenously in patients with a tendency toward pulmonary congestion and edema, because of cardiac, pulmonary, central nervous system, or renal disease, these infusions should be given at slower rates and with caution.

AUTHORS.

Battro, A., and Labourt, F. E.: Contribution to the Study of Functional Pulmonary Capacity in Certain Cardiopathies (Method of Spirography). *Rev. argent. de cardiol.* 8: 317, 1941.

The functional pulmonary capacity of 30 cardiac patients was measured by determining the oxygen consumption and respiratory volume while breathing air or oxygen, during rest and during exercise. The criteria adopted for the classification in 4 degrees of respiratory insufficiency are described.

Eighteen of the 30 patients had mitral stenosis; the other 12 had various heart diseases with manifest signs of left ventricular failure.

In the rest, 73.3 per cent of the patients showed no sign of functional pulmonary insufficiency.

During exercise an arterial unsaturation of oxygen was manifested in 66.6 per cent of the patients.

The causal factors in the respiratory insufficiency of cardiac patients are discussed.

AUTHORS.

Cournand, A., Ranges, H. A., and Riley, R. L.: Comparison of Results of the Normal Ballistocardiogram and a Direct Fick Method in Measuring the Cardiac Output in Man. *J. Clin. Investigation* 21: 287, 1942.

The accuracy of the ballistocardiographic method of cardiac output determination was tested by comparing it with a method based on the Fick principle.

The technique of the direct Fick determination, involving catheterization of the right auricle, was discussed.

Fourteen almost simultaneous pairs of cardiac output determinations were compared, in which the following criteria were satisfied: pulse rate varied less than 4 beats; ballistocardiograms were normal in shape, regular, and easily readable; cardiac output calculated separately from oxygen consumption and from carbon dioxide elimination checked closely.

Cardiac output as determined by the direct Fick method was found to be larger by 18.5 per cent than the value calculated from the ballistocardiogram, using Bazett's tables for internal cross-section of the aorta.

Using figures for aortic cross-section obtained by diodrast visualization in 5 cases, cardiac output as calculated from the ballistocardiogram was found to check very closely with the values obtained by the direct Fick method, the average difference being 3.5 per cent.

On the basis of these findings, it is suggested that the accuracy of cardiac output determination with the ballistocardiograph may be improved by correcting the calculated value by an amount equal to the average error found experimentally, i.e., 18.5 per cent, or by introducing in the formula a value for internal cross-section of the aorta on diodrast visualization.

AUTHORS.

Kerwin, A. J.: Pulmonocardiac Failure as a Result of Spinal Deformity: Report of Five Cases. *Arch. Int. Med.* 69: 560, 1942.

The clinical and pathologic characters of 5 cases of pulmonocardiac failure in extreme spinal deformity are described.

The significant pathologic lesions are the result of pulmonary hypertension, which eventually leads to right-sided heart failure and appears to be due to mechanical interference with respiratory function.

AUTHOR.

Book Reviews

ELECTROCARDIOGRAPHY: By Louis N. Katz, M.D., Director of Cardiovascular Research, Michael Reese Hospital, and Assistant Professor of Physiology, University of Chicago. Lea and Febiger, Philadelphia, 1941, 580 pages, 402 illustrations, \$10.00.

This book is not a compilation of the accumulated knowledge on the subject but is more especially an expression of the opinions of the author. It seems at times that the author's observations and hypotheses are given undue prominence when one considers the wide scope of the literature with its divergent opinions. His opinions are frequently at variance with widely accepted hypotheses and diagnostic classifications, and one does not always feel that the reasons for thus diverging from the generally accepted views are compelling. Several features particularly attract the attention of the reviewer because they seem to represent a backward step in the study and interpretation of the electrocardiogram. In discussing the QRS group the author writes practically a new nomenclature and lists seven different varieties of QRS. He recommends dropping the term "axis deviation" and introduces in its place two other terms. The diagnostic distinction made between the records which are said to indicate "axis shift" and those indicating "ventricular preponderance" does not rest upon any experimental evidence and is, in fact, little more than a hypothesis.

There are a surprising number of records with very slight and seemingly insignificant variations from the normal which are considered by the author as "definitely abnormal" or as "borderline"; such, for instance, are Figs. 94 B, 94 C, 72 A, and 209 B. There is doubt whether what is here called progressive chronic coronary insufficiency should not be called progressive myocardial degeneration. The myocardium is nearer to the electrocardiogram than the coronary arteries are, and it is quite possible to name conditions other than coronary disease that might be responsible for the electrocardiographic changes in question. There is considerable doubt whether such diseases as pericarditis, pulmonary embolism, uremia, cardiac trauma, severe acute anemia, and dissecting aneurysm should be regarded as affecting the electrocardiogram by the mechanism of coronary insufficiency. There is no question that these conditions are often associated with abnormalities of the waves, but here again it is the myocardium which influences the record, and it is probably this that is primarily affected by the disease. The author's hypothesis that the physiologic mechanism is one of coronary insufficiency does not seem well founded.

The statement that scar tissue in the heart does not lead to electrocardiographic changes unless it has interrupted important pathways or has interfered with the nourishment of a part of the myocardium is certainly one which has not been substantiated by adequate pathologic studies and, as an unqualified statement, is very likely to be wrong. It is an interesting theory that broad, notched P waves may be caused by intra-auricular block, but such a theory cannot be accepted without more definite pathologic evidence than has ever been demonstrated. Other equally satisfactory theories as to the abnormal form of these aberrant P waves have previously been advanced.

The author refuses to accept the localization of bundle branch block which has been established as a result of recent animal and human experiments and the

study of precordial leads. In its place he suggests a classification based upon certain more or less striking features of the curves in question. This is regrettable, for it seems that the localization of the site of bundle branch block has been established in a manner satisfactory to the majority of cardiologists. The fundamental points of distinction between the curves of right and left bundle branch block seem well enough established at present to warrant universal adoption, making such analyses of the records as suggested by the author totally unnecessary.

The sections on muscle physiology and anatomy are excellent in many respects, but it is regrettable that so often the individual opinion of the author is expressed without mention of the fact that it differs from that which is generally accepted. There is an interesting series of electrocardiograms on normal infants and young children, showing the progressive changes that may be found with increasing age. The numerous illustrations of the progressive effect of digitalis upon the T wave afford an excellent opportunity to study this feature.

The section devoted to the description of the changes associated with myocardial infarction and the healing which follows is one of the best parts of the book. The illustrations are numerous and give a complete picture of the development of the S-T and T-wave changes. Forty-four figures indicate the progressive changes in serial electrocardiograms taken over varying periods of time both before and after cardiac infarction. One can heartily agree with the author in his statement that the commonest error in electrocardiographic interpretations is the belief that the electrocardiogram can show the extent of myocardial damage.

There is an excellent and complete section on the cardiac arrhythmias. The author, as is usual, introduces a number of new terms and new subdivisions of old categories. In these instances the subdivisions seem to have a clearly definable basis and may be found helpful for more general use. It is doubtful whether the distinction between coarse and fine auricular fibrillation is of much importance, but, if it is important, a definite dividing line should have been suggested.

The chief value of the book to the beginner lies in the large number of illustrations and descriptive text. The difficulty for the beginner lies in the necessity of learning a large number of new terms, which he probably will not encounter in the vocabulary of other authors, and in the confusion resulting from the discarding or superseding of many commonly accepted definitions. The large number of illustrations are also valuable to the more advanced student who may wish to find records of certain rare conditions. The illustrations of electrical alternans will be particularly interesting to such a reader.

HAROLD E. B. PARDEE.

EXERCISES IN ELECTROCARDIOGRAPHIC INTERPRETATION: By Louis N. Katz, M.D., Director of Cardiovascular Research, Michael Reese Hospital, and Assistant Professor of Physiology, University of Chicago. Lea and Febiger, Philadelphia, 1941, 222 pages, 128 illustrations, \$5.00.

This volume affords an opportunity to review a large number of electrocardiograms in connection with certain salient features of the clinical conditions which have been selected by the author. Accompanying each record there is first a description of the individual features of the record, secondly, an interpretation of these features in terms of heart muscle physiology and pathology, thirdly, a brief picture of the patient's symptomatology and diagnosis, and, finally, what is called a correlation, which is a discussion of the contributions of the electrocardiographic record to an understanding of the clinical picture. It would be necessary for one to have previously read the parent book, because the author's terminology, which differs from that commonly accepted, is used throughout. One would not know,

for instance, the meaning of "left ventricular preponderance of the first type" nor the meaning of "a QRS of the Q type." Having mastered the author's terminology, however, there will be much to learn from a perusal of these records and the accompanying text for one who has not had much experience in interpreting electrocardiograms.

HAROLD E. B. PARDEE.

CLINICAL CARDIOLOGY, WITH SPECIAL REFERENCE TO BEDSIDE DIAGNOSIS: By William Dressler. Paul B. Hoeber Inc., New York, 1942, 692 pages, 108 illustrations.

This is a well-arranged, readable, complete book and the illustrations are well chosen. It is a clear, concise, ex-cathedra exposition of clinical cardiology. Throughout, the author has accepted the newest viewpoints. This is especially noticeable in his discussion of the pathogenesis of hypertension, of the natural history of rheumatic infections, and of the etiology of aortic stenosis.

The book has a very certain, but by the same token limited, appeal, in that it is written for senior students, young graduates, and general practitioners, especially for use during a post-graduate course. It is too advanced for younger students and too elementary for advanced students. It fails to point out and discuss the various aspects of the many problems which still await solution, and, above all, the author has chosen to omit all references to the literature. This is the worst aspect of the book, for every student should, as early as possible, be encouraged to seek the source records for himself. By this omission also the field of cardiological history is completely ignored. The modern cardiologist might find that the author overemphasizes physical diagnosis to the detriment of the newer, modern means of diagnosis; the electrocardiograph and the fluoroscope are no longer special instruments, but aids in physical diagnosis as indispensable as the stethoscope and the sphygmomanometer.

One must decidedly disagree with the author when he says (p.VI) that evaluation of electrocardiographic data has done more harm than good; when that happens it is due to poor judgment, and the complaint might, with the same justification (or lack of it), be lodged against stethoscopy or physical diagnosis; think of the interpretations given to "murmurs."

The reviewer also believes that the student for whom this book is meant would like to know, at least briefly, what kymography, phonocardiography, and other modern methods are and what they contribute, even though they are not of fundamental importance.

The ex-cathedra method of exposition has led to a number of statements which represent the author's opinion rather than what is generally accepted. Many of his views on myocardial infarction differ from those of other authorities; he fails to recognize "degenerative heart disease" as an etiological group comparable to infectious heart disease, and his use of the term "angina pectoris" is particularly distressing, in that he does not clearly distinguish between the pain of transitory anoxemia and that of myocardial infarction as suggested by the "nomenclature" (New York Heart Association), but he calls all pain from myocardial ischemia, angina pectoris.

A number of statements which appear so new and unusual are made without quoting his authority. Some seem to be suspended in thin air; for instance, when he says that about 50 per cent of the extrasystoles accompany organic heart disease (p. 235), it is necessary to state whether he obtained his statistics from a recruiting office, an office practice, or a hospital ward.

Of frank omissions there are not many beyond what may be expected by the limitation of the scope of the book. There are, however, some facts missing which should not be omitted even from an elementary textbook. The author does not mention xanthopia as a sign of overdigitalization; Wenckebach's periods, once mentioned, should be explained; the early combination of digitalis and diuretics in congestive failure. The figure giving the incidence of positive serologic reactions in syphilitic heart disease is not in the book. The importance of venous pressure measurements in the evaluation of cardiac function is not duly emphasized; the discussion of cardiac aneurysm can be found only by a thorough perusal of the text—it should be included in the index. There is no mention of the symptomatic effects of sympathectomy in hypertension, which, though difficult to explain, are real enough to be included in the effects of the operation. These are, after all, minor defects in an excellent book. Outweighing these criticisms is the fact that students were more than usually attracted to the volume.

On the whole, the book is a contribution to our didactic cardiological literature and should prove popular with the readers for whom it is meant.

JULIUS JENSEN.

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**Executive Committee.*

American Heart Journal

VOL. 24

DECEMBER, 1942

No. 6

Original Communications

HYPERTENSION AND CARDIAC RUPTURE

A CLINICAL AND PATHOLOGIC STUDY OF SEVENTY-TWO CASES, IN THIRTEEN OF WHICH RUPTURE OF THE INTERVENTRICULAR SEPTUM OCCURRED

HUGH A. EDMONDSON, M.D., AND HAROLD J. HOXIE, M.D.
LOS ANGELES, CALIF.

THE literature on cardiac rupture is replete with names great in medical history. The condition was first described by William Harvey,¹ in 1647. By 1765, Morgagni² was able to collect autopsy records of ten patients who had died from this cause, and added one that he had observed. Morand,³ Bland,⁴ Cruveilhier,⁵ Adams,⁶ Hodgson,⁷ and Barth⁸ also made contributions to this subject.

Benson, Hunter, and Manlove,⁹ in 1933, reviewed the subject and traced clearly the evolution of our knowledge of spontaneous rupture of the heart. These authors divided the accumulation of our present knowledge of this subject into three periods. In the first period, previous to 1861, the authors¹⁻⁸ failed to observe that coronary sclerosis and thrombosis, with consequent myocardial infarction, were the common underlying causes of rupture. The areas of infarction through which rupture occurred were undoubtedly noted but were regarded as areas of fatty degeneration. Malmsten¹⁰ recorded, in 1861, his observations of a ruptured heart in which he described an area of softening and rupture caused by an old thrombus in the anterior descending coronary artery. After this, many others made similar observations. The second period ended in 1896 with a review by René Marie,¹¹ who correctly stressed the relationship of coronary sclerosis and thrombosis to myocardial infarction and rupture.

We are at the present time in the third period, during which some progress has been made in the study of the coronary arteries, their collateral circulation, and the usual sites of thrombosis (Blumgart, Schlesinger, et al.^{12, 13, 14}). Many cases of interventricular rupture have been reported, together with criteria for the clinical diagnosis. Among

From the Department of Pathology, School of Medicine, University of Southern California, the Department of Medicine, College of Medical Evangelists, and the Laboratory of the Los Angeles County Hospital, Los Angeles, California.

Received for publication May 2, 1942.

the factors considered in cardiac rupture, softening of the myocardium after coronary thrombosis has received the greatest emphasis. Little discussion has been given to the bursting power of the intraventricular pressure, although it seems to have been considered necessary. Krumbhaar and Crowell¹⁵ mention that a rise in blood pressure during sleep, as demonstrated by MacWilliam,¹⁶ may be the exciting cause of rupture. Beresford and Earl¹⁷ add that a rise in blood pressure during defecation may precipitate rupture. The possible role of arterial hypertension after infarction is mentioned only by Mallory, White, and Salcedo-Salgar,¹⁸ who make the following statement: "Another factor of importance in this connection is the intraventricular pressure. The higher this pressure, the more likely rupture is to occur." In their study of the speed of healing of myocardial infarction in seventy-two patients there were eight instances of rupture. In two of the eight, hypertension was present after infarction had occurred. These authors also say that the enzymatic action of polynuclear leucocytes in the area of necrosis may tend to reduce its resistance.

Since only a small percentage of infarcts undergo rupture, the factors that contribute to the mechanism deserve special consideration. Among these may be age, sex, increase of subepicardial fat, opposing pull of muscle bundles, and hemorrhage into the area of infarction.

The present study, which was started in 1934, was undertaken because it seemed to us from our autopsy experience that rupture often followed the first attack of coronary thrombosis in persons who had hypertension and some degree of cardiac hypertrophy, and whose hypertension persisted after infarction. In most of these hearts there appeared to be a sufficient amount of undamaged myocardium outside the area of infarction to maintain a relatively high intraventricular pressure. We have attempted by a study of available material to find out whether or not a correlation exists between blood pressure and rupture. In addition, we have considered the possible relationship of scarring of the myocardium and heart weight to rupture.

MATERIAL

This study is based upon the records of all patients who were found to have rupture after myocardial infarction caused by coronary disease in a series of 25,000 consecutive autopsies which were performed at the Los Angeles County Hospital from July, 5, 1924, to August 15, 1941. All instances of recent, unhealed infarction, without rupture, among these autopsies, were used as a control group.

A study was also made of the records of 100 patients who had convincing clinical and electrocardiographic evidence of acute myocardial infarction and recovered sufficiently to leave the hospital. These records were taken in consecutive order from the files of our department of electrocardiography.

STATISTICAL SURVEY

Among the 25,000 autopsies, 865 (3.4 per cent) hearts were found to have one or more unhealed infarcts. Among the 865 there were 72 (8.3 per cent) that had ruptured (0.29 per cent of the total number of autopsies). The rupture of the myocardium was in an area of recent infarction in each instance. In the group of 72 ruptured hearts, only 19 (26.3 per cent) contained scars, whereas there were scars in 58.4 per cent of the unruptured hearts with unhealed infarcts.

The age incidence by decades of those who had infarction alone, as compared with those who had rupture, is shown in Fig. 1. The high incidence of rupture in the seventh and eighth decades closely parallels the incidence of infarction in these decades. The difference shown in the eighth decade is not statistically significant. There was no significant difference in age incidence between those with and those without myocardial scars.

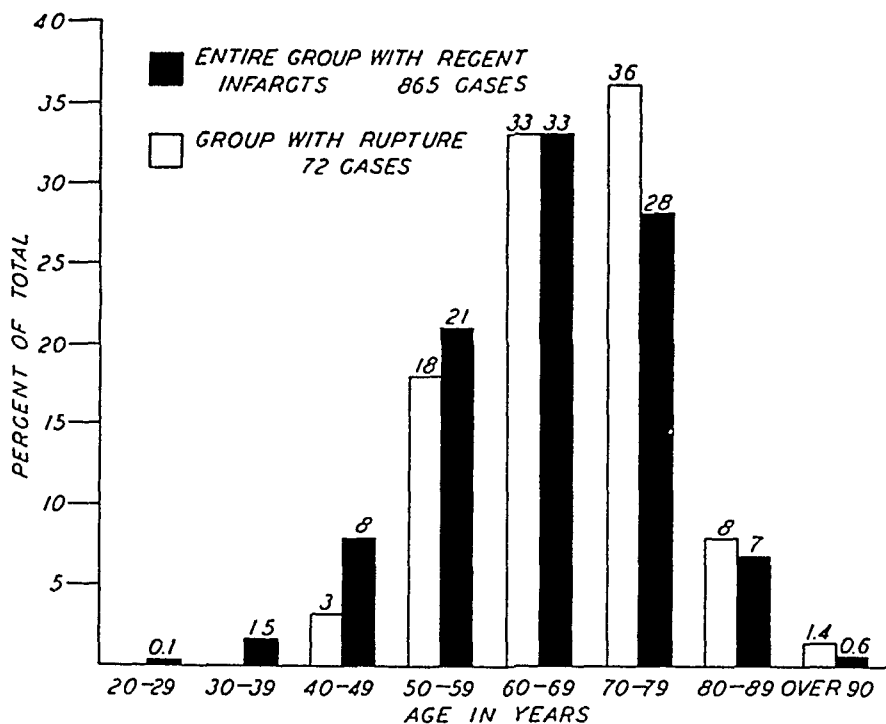


Fig. 1.—Age distribution of cardiac rupture, compared with that of fatal myocardial infarction.

Of the 865 patients who had one or more unhealed myocardial infarcts, 601 (69.4 per cent) were males. Of the 72 whose hearts ruptured, only 40 (55.5 per cent) were males. This difference is statistically suggestive.

The seasonal variation of incidence of rupture of the heart did not differ significantly from that of myocardial infarction. The frequency of obesity in the group with ruptures was practically the same as that among those who had infarcts that did not rupture.

In the first half of the records studied, covering the period from July, 1924, to November, 1935, there were 266 instances of myocardial infarction with 23 (8.6 per cent) ruptures; but in the second half, 599 instances of infarction and 49 (8.2 per cent) ruptures were observed. Thus it appears that the increased incidence of myocardial rupture is caused by a proportional increase in the number of infarctions of the heart in recent years.

PATHOLOGY

Gross.—A pericardial cavity distended with blood at necropsy has always aroused the interest of pathologists. Some consider it a rare occurrence. By far the most common cause of hemopericardium is myocardial rupture. In the autopsies reported here, the amount of blood in the pericardial cavity was usually estimated by the autopsy surgeon. These estimates varied from 150 to 700 c.c., but the majority were recorded as being from 200 to 250 c.c. Because of the inelastic nature of the parietal pericardium, this volume is probably sufficient to cause tamponade. This differs from chronic disorders, such as tuberculous pericarditis, in which the parietal pericardium has had time to become greatly distended, and, in consequence, a liter or more of fluid may collect in the cavity.

TABLE I

SITE OF RUPTURE	SITE OF CORONARY THROMBOSIS					
	NO.	L.D.	L.C.	NONE SEEN	R.C.	MULTIPLE
Left ventricle, anterior	37	33		3		L.D. & R.C.
Left ventricle, posterior	10	1	3	1	5	
Left ventricle, lateral	5	1	4			
Right ventricle, anterior	3	2				L.D. & L.C.
Right ventricle, posterior	1					L.D. & L.C.
Not recorded	3		1	2		
Interventricular septum	13	5		2	5	L.D. & L.C.
Totals	72	42	8	8	10	4

L. D., Left Descending.

L. C., Left Circumflex.

R. C., Right Coronary.

The sites of rupture, with the corresponding location of thrombosis in the coronary arteries, are seen in Table I. It is of interest that the left anterior descending branch is the artery most often involved (58.3 per cent), and that, after its occlusion, ruptures occurred in all portions of the ventricles and septum except the posterior portion of the right ventricle. In one instance (Autopsy No. 22821), the area of infarction and rupture was in the posterior wall of the left ventricle, whereas the thrombosis occurred in the anterior descending branch of the left coronary. In the group in which interventricular septal rupture occurred, the anterior descending and the right coronary were involved an equal number of times.

Our interest in the relationship of blood pressure to rupture prompted us to study the size of the infarcts. It is logical to assume that the blood pressure after infarction depends to some extent on the proportion

of the uninvolved muscle to the ischemic portion. The size of the infarcts was recorded in 35 ruptured hearts. The dimensions of these varied from 2 x 1 cm. to 11 x 9 cm. In 25 of the 35 specimens the greatest dimension of the area of infarction was 5 cm. or less. In three in which the infarct was 50 sq. cm. or larger, the highest blood pressure recorded after occlusion was 130/90. These figures may be compared with those in a similar group without rupture. The size of the infarcts in 35 unselected instances in which measurements were available varied from 2 x 1 cm. to 10 x 8 cm. Nineteen were 5 cm. or less in their greatest dimension, and, correspondingly, there were more of the larger infarcts. In six the infarct was 50 sq. cm. or larger, and the blood pressure in this group of patients varied from unobtainable to 138/94. In five of these six the blood pressure was normal or subnormal, in spite of the fact that all five hearts were enlarged.

The following case illustrates how early even a small infarct may rupture when the intraventricular pressure is high.



23266

Fig. 2.—Rupture of lateral wall of left ventricle through a small recent infarct. (Aut. No. 23266.)

Autopsy No. 23266, J. I., a white man, aged 76 years, entered the hospital Dec. 2, 1939, because of severe frontal headaches and failure of a recent enucleation wound of the eye to heal. Pyuria and hypertension (190/110) were first discovered in 1938. On entry the temperature was 99° F., the pulse rate, 84, and the respiratory rate, 18. The blood pressure was 210/100. The urine contained albumin (+++). The blood creatinine was 10.4 mg. per hundred cubic centimeters. The patient became irrational, complained once of shortness of breath, and died suddenly twenty-four hours after admission.

The necropsy was performed fourteen hours after death. The essential changes were in the heart and kidneys. The pericardial cavity contained 110 c.c. of blood, the heart weighed 370 grams, and a linear tear was present on the lateral surface

of the left ventricle (Fig. 2). The rupture had occurred through a small infarct, 4×2 cm. The coronaries were sclerotic, and a recent thrombus completely occluded the left anterior descending branch. The kidneys were severely scarred; the right weighed 30, and the left, 60 grams. On histologic examination, the renal changes were those of chronic pyelonephritis and extreme atrophy. Microscopic study of the myocardium disclosed only a few areas of early necrosis of muscle fibers (Fig. 3). A few interstitial hemorrhages were present along the course of the rupture. In some areas the tear had apparently occurred through muscle in which there was not yet histologic evidence of necrosis.

We believe that such a rupture, occurring in a small infarct so soon after occlusion of the artery, is best explained by the high blood pressure.

The course of the tear in the myocardium was usually somewhat tortuous, but the records in this regard were incomplete. The length of the tear in the epicardium varied from 0.3 cm. to 3.3 cm.; the average was 1.6 cm. The endocardial tears were smaller and were difficult to measure. Many authors mention their frequency near the base of the anterior papillary muscle. This was mentioned only rarely in our records.

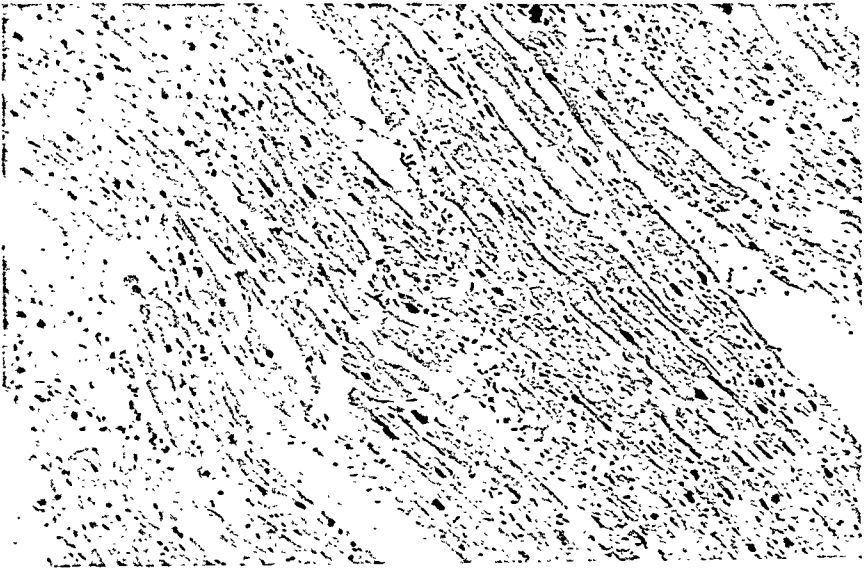


Fig. 3.—Patchy necrosis of myocardium adjacent to rupture seen in Fig. 2 ($\times 105$).

Sixty-six of the ruptured hearts were weighed. The average weight was 458.3 grams. Fifty-two (78 per cent) weighed 400 grams or more. We have considered that a cardiac weight of 400 grams or more indicates hypertrophy. The average weight in the control group of 733 infarcted hearts, without rupture, was 488 grams and 594 of these (81 per cent) weighed 400 grams or more.

Scars were seen in 19 hearts, as mentioned above. In 12 the scarring was diffuse in nature; in 7 the scars were circumscribed and were interpreted as indicating old infarcts. In two of these a recent infarct and rupture had occurred in the center of an old infarct. Six of the seven hearts with old infarcts weighed 425 grams or more, and hypertension was present in five of the patients after occlusion.

The thickness of the left ventricle was recorded in 37 cases. The range was from 10 to 25 mm., and the average was 15.4 mm. Twenty-seven were 14 mm. (the borderline for hypertrophy) or more in thickness.

Increase of subepicardial fat has often been mentioned as a predisposing cause of rupture. In these records the amount of fat was rarely mentioned, but in the experience of the authors, which includes 16 of the hearts in this series, an increase of subepicardial fat appears to be associated fairly frequently with cardiac rupture.

No conclusions could be drawn from the descriptions of the size of mural thrombi, because in more than half of the hearts thrombi had not yet formed, or at least they were not mentioned in the protocols.

Microscopic Observations.—Sections of the myocardium were available for histologic study in 41 of the cases of rupture. They were studied from the standpoint of establishing criteria which would differentiate infarction with rupture from other myocardial infarctions. Only two observations of suggestive value were made. In 22 of the 41 hearts there was a complete, smudgy type of necrosis which involved all the tissue over a wide area. The other observation substantiates one made long ago by many students of the problem. This was widespread, heavy infiltration of the area of infarction with polymorphonuclear leucocytes, and it was found in 18 cases. This may resemble an abscess (Bresnihan¹⁹). It is well known that necrotic polymorphonuclear leucocytes liberate a proteolytic enzyme. This may conceivably add to the softness of an area of infarction.

In comparing these changes with those in the hearts which were infarcted but unruptured, the same type of necrosis and heavy infiltration with polymorphonuclears was seen, but in a smaller proportion of specimens. Undoubtedly the appearance of an infarct will depend on the time that has elapsed since the onset, and, as rupture is likely to occur when the infarct is softest (three to twelve days), the observed changes may be what one should expect to find. However, on gross examination there appears to be a great variation in the degree of softening of infarcts of the myocardium which is not entirely dependent on the time element. In the literature concerning rupture, many authors have mentioned the ease with which the infarcted muscle may be torn with the finger tip. On the contrary, rupture can occur in spotty infarcts and in those in which little softening has occurred (Autopsy No. 23266). Careful gross and histologic study of all infarcts, combined with antemortem blood leucocyte counts, would be helpful in ascertaining the relation of leucocytic infiltration to softening.

Infarction of the endocardium and thrombosis of the Thebesian vessels as further factors in weakening the heart wall were also searched for, but no conclusive evidence was obtained. Rarely did the area of infarction include the endocardium. In the instances in which there was thrombosis of the Thebesian vessels, it was a part of a mural thrombus. The number of instances in which the endocardium was not involved by the necrosis in myocardial infarction was surprising.

A variety of renal changes was observed. Sections of kidney were available in 53 of the group with cardiac rupture. Seven of 47 persons who had cardiac hypertrophy and/or hypertension had kidneys of normal appearance. All the rest had evidence of hypertensive disease. Most common was diffuse arteriolar nephrosclerosis (35 cases). Chronic pyelonephritic, contracted kidneys were present in three. There was one instance of diabetes and intercapillary glomerulosclerosis (Kimmelsteil-Wilson's disease) and one of chronic glomerulonephritis.

CLINICAL DATA

Statistics regarding the available blood pressure measurements in three groups of patients are recorded in Table II. The first is a group of 100 patients who survived and recovered sufficiently to leave the hospital after myocardial infarction had been diagnosed from the clinical and electrocardiographic manifestations. The second group consists of those who had unhealed and unruptured infarcts in their hearts. The blood pressures were taken after infarction. The third is the group with ruptured myocardial infarcts. The blood pressures used were those taken between the time of infarction and rupture.

For uniformity, the following method of tabulating blood pressures was used. When more than one measurement was recorded on the chart, the average was used. The mean blood pressure was used in those instances in which the systolic pressure was above the indicated amount of 140 or 160 and the diastolic was below 90 or 100, and in instances of a higher diastolic and a lower systolic. With the exception of those whose diastolic pressures were below 70 mm. Hg, those with a mean blood pressure of 115 were considered to have a blood pressure of 140/90, and those with a mean pressure of 130 were included as having a blood pressure of 160/100.

TABLE II

	TOTAL	B.P. 140/90 OR ABOVE		B.P. 160/100 OR ABOVE		AVER- AGE SYS- TOLIC MM. HG.	AVER- AGE DIAS- TOLIC MM. HG.
		NO.	%	NO.	%		
Group I—Nonfatal myo- cardial infarction	100	23	23	9	9	125	78
Group II—Fatal infarc- tion, unruptured	657	210	32	118	18	128	81
Group III—Fatal infarc- tion, ruptured	62	39	63	20	32	148	93

The greater incidence of hypertension in the group of patients with ruptured hearts is significant, particularly when 140/90 mm. Hg is taken as the hypertensive level. The average blood pressure in this group also is significantly higher.

The data on Groups II and III are arranged in Table III to show the frequency of rupture of the heart when the blood pressure is low and

when it is high. It appears from this tabulation that, in the presence of myocardial infarction, blood pressures above 140/90 are as likely to be associated with rupture of the heart as pressures above 160/100.

TABLE III

	MYOCARDIAL INFARCTION		
	TOTAL	RUPTURED	
		NUMBER	% OF TOTAL
Blood pressure below 140/90	470	23	4.9
Blood pressure 140/90 or above	249	39	15.7
Blood pressure below 160/100	581	40	6.9
Blood pressure 160/100 or above	138	20	14.5

Table IV is designed to ascertain whether there is any correlation between cardiac size and tendency of the infarcted heart to rupture. The notable facts shown are that the proportion of rupture is highest (25 per cent) in the group with small hearts and hypertension, and lowest (4 per cent) in the group with large hearts and low blood pressure.

TABLE IV

	NO RUPTURE (644 CASES)		RUPTURE (58 CASES)		TOTAL	% RUP- TURED
	NUMBER	%	NUMBER	%		
Heart weight— 400 Gm. or more	187	29	31	53	218	14
B.P. 140/90 or above						
B.P. under 140/90	354	55	14	24	368	4
Heart weight— under 400 Gm.	21	3	7	12	28	25
B.P. 140/90 or above						
B.P. under 140/90	82	13	6	10	88	7

In the records of 66 of the patients with ruptured hearts, sufficient data were present to establish the date of an attack that could be reasonably assumed to be the result of coronary occlusion and infarction of the heart. The interval from infarction to rupture was calculated from this date. The majority of the ruptures (52, or 78.8 per cent) occurred from the third to the twelfth day after infarction, and 98.5 per cent on or before the sixteenth day. Six instances of rupture were thought to have occurred one day after infarction, and one on the twenty-ninth day. The average calculated time from infarction to rupture was 7.4 days.

The records of 16 patients indicated that there was a return or marked increase of pain at the time of the rupture. Only 6 patients were recorded as having exerted themselves at the time of, or shortly preceding, the rupture, and in each instance the exertion was mild. Five patients died during sleep.

Data regarding duration of life after rupture were present in 56 records. In this respect the patients are clearly separated into two groups,

namely, those whose heart wall ruptured into the pericardium, and those whose rupture was of the interventricular septum. Of the former group of 45 patients, it is recorded that 24 died suddenly, 18 died within a few minutes, 2 lived for fifteen minutes, and 1 lived for three hours. Numerous small perforations, rather than a single tear, were noted in the wall of the heart of the last-mentioned patient.

Interventricular Septal Rupture.—It was possible in 11 of the 13 patients who had interventricular septal rupture to ascertain the length of life after the rupture. Ten of these patients lived from nine hours to seven days, with an average survival period of 2.25 days. One patient lived for several months after the rupture (Fig. 4). In 6 cases, blood pressures were taken between the time of infarction and rupture, and after rupture of the interventricular septum. The respective averages were 160/100 and 85/60, an average decrease in pressure of 75 mm. Hg systolic and 40 mm. Hg diastolic. A precordial systolic murmur was observed in 11 of the 13 patients who had rupture of the interventricular septum. In 3 of these patients, all within the last two years, a correct ante-mortem diagnosis was made.

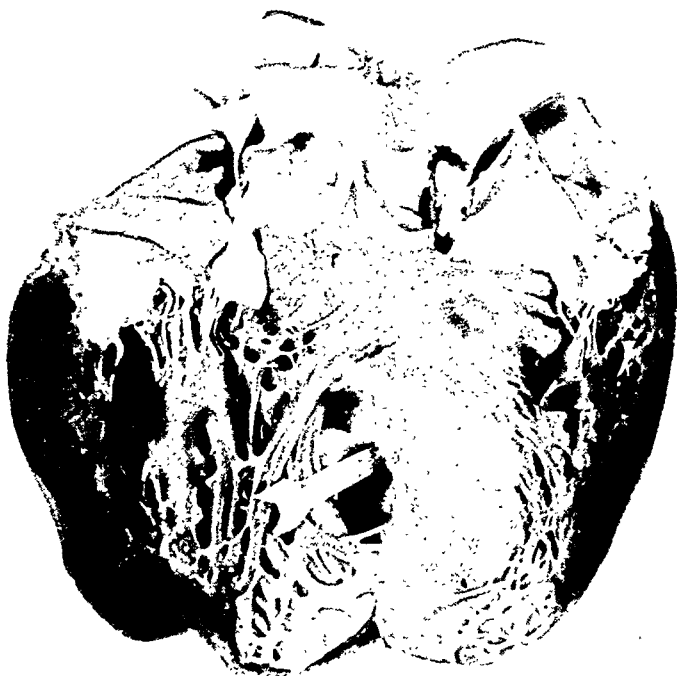


Fig. 4.—Old healed interventricular septal rupture. (Aut. No. 11590.)

COMMENT

Comparison of the incidence of rupture of the heart in various series of autopsies must, of course, take cognizance of the type of patients comprising each series. From an institution which cares predominantly for elderly patients with mental disturbances, Beresford and Earl¹⁷ reported an incidence of 31 ruptures among 2,374 autopsies. This is an

even higher incidence than that reported by Benson, Hunter, and Manlove,⁹ who found 27 ruptures among 2,112 coroner's autopsies. Krumbhaar and Crowell,¹⁵ in 1925, reported only 7 ruptured hearts among 16,000 autopsies at the Philadelphia General Hospital. They also quoted Romeik's Munich series of 13,000 autopsies, in which 7 ruptured hearts were found, and a series from Leipzig in which 9 ruptures were present in 8,000 autopsies. The average incidence in these three series was 0.06 per cent. This is much less than the 0.28 per cent of 4,657 autopsies on general hospital and private patients reported by Benson, Hunter, and Manlove,⁹ in 1933. The above reports are not limited to rupture of the heart wall through myocardial infarcts, and they do not give the total number of myocardial infarcts in the autopsy series. The relatively great frequency of cardiac rupture in our series (0.29 per cent) bears a certain more or less constant relationship to the incidence of myocardial infarction among patients who die in the Los Angeles County Hospital.

Before making this study we were impressed by the increased number of ruptures of the heart in recent years. This study reveals, however, that it is not the frequency of rupture in infarcted hearts that has increased, but rather the incidence of myocardial infarction. The great increase in frequency of fatal myocardial infarction in the second half of our group is most impressive. In the first 12,500 autopsies there were 266 instances of myocardial infarction. In the second 12,500 autopsies myocardial infarction was present in 599. The explanation is not apparent.

The significantly lower incidence of gross scarring among the ruptured, as compared with the unruptured, hearts in this group has an important bearing on the factors in rupture of a heart wall. Only 1 in 25 of the infarcted hearts which contained scars ruptured, whereas 1 in 6 of the unscarred hearts ruptured. It thus appears that an infarct is about four times as likely to rupture in a heart in which the coronary circulation has previously been adequate. One reason may be that in unscarred hearts the blood pressure after infarction is maintained at a higher level because there is a greater mass of undamaged myocardium. The average blood pressures in these groups, however, do not support this assumption. We believe the most important reason that scarred hearts are less likely to rupture is the fact that collateral circulation is greatly increased in these hearts, so that subsequent areas of infarction may be less likely to be soft and friable. Another reason may be that, in an area of infarction which contains fibrous tissue as a result of previous coronary insufficiency, the fibrous elements may be resistant to ischemia, thus adding support to the necrotic muscle.

Although it must be admitted that blood pressures taken some time before rupture of the heart may not indicate the exact pressure at the time of rupture, we believe that in a fairly large group of patients these blood pressure records are of real significance. The incidence of elevated blood pressure in the group with ruptured infarcts of the heart was

about twice as great as among those who died with unruptured infarcts, and about three times as great as in the group that survived myocardial infarction.

From the data in Table III it appears that the victims of myocardial infarction who die are two or three times as likely to die of a ruptured heart if the blood pressure is high. Only 23 (4.9 per cent) of the 470 patients with blood pressure below 140/90 suffered rupture of the heart, whereas 39 (15.7 per cent) of the 249 patients with blood pressures above this figure suffered rupture of the heart. Practically the same proportions obtain when 160/100 is taken as the lower level of high blood pressure.

It must be remembered that arterial blood pressure is indicative of the function of the left ventricle; therefore, our data regarding blood pressure are hardly applicable to the study of rupture of the right ventricle. The present series of 72 ruptures contains only 4 instances of rupture through the right ventricle.

Tabulation of the blood pressures of those whose hearts weighed less than 400 grams and those whose hearts weighed more than 400 grams (Table IV) reveals that large hearts, with low blood pressure, are least likely to rupture, and that small hearts in patients who have hypertension are most likely to rupture.

A combined study of the gross and microscopic observations on ruptured hearts after coronary thrombosis, plus the evidence obtained from blood pressure readings after infarction, leads us to feel that the chief factors which determine rupture are softening of the infarct and height of intraventricular pressure. Either factor may be predominant. A soft, friable infarct may rupture with normal intraventricular pressure. On the other hand, a small, spotty infarct may rupture when the intraventricular pressure is high. The high incidence of rupture after infarction in mentally defective patients reported by Beresford and Earl¹⁷ may be ascribed to the fact that such patients are less cognizant of pain and therefore exert themselves unduly. It seems reasonable to assume that the height of intraventricular pressure would vary inversely as the size of the infarct. Our data suggest such a correlation, for few hearts with infarcts larger than fifty square centimeters were capable of supporting an elevated blood pressure. The factors which determine the degree of softening of an infarct of the myocardium are complicated, and one's reasoning is beset by unknown factors. The degree of anoxia of the area is a factor of prime importance. This is determined by the extent of the collateral circulation, which may vary greatly. Increased subepicardial fat and fatty infiltration of the muscle tend to increase softness in an area of necrosis. The opposing pull of muscle bundles may increase a tendency to tear. Heavy infiltration of polymorphonuclear leucocytes and subsequent disintegration, necrosis, and liberation of liquefying enzymes may well increase the softness of an infarcted area. The reason for the variation in degree of infiltration with neu-

trophils is an unsolved problem. Rosenbaum and Levine²⁰ find that the prognosis is poorer in patients who have high leucocyte counts, but do not mention the level in those whose hearts ruptured.

Interventricular Septal Rupture.—The interventricular septum was ruptured in 13 of the 72 hearts. This seems to be a surprisingly large number, in view of the fact that the condition has previously been reported in only 23 patients.²¹ Benson, Hunter, and Manlove⁹ reported 40 ruptured hearts, but only one was ruptured through the septum. Beresford and Earl¹⁷ reported 46 ruptured hearts, but none was ruptured through the septum. An ante-mortem diagnosis of interventricular septal rupture was reported in 4 of the 23 patients mentioned above. In our group it was made in 3 of the 13 patients. These three correct diagnoses were made during the last two years. The diagnostic significance of a loud precordial systolic murmur which appears suddenly in a person who has recently suffered a coronary occlusion is now well recognized by the attending and resident staffs of this hospital. The clinical course of the patients with rupture of the interventricular septum differed from that of those with other ruptures in that the patients lived longer (nine hours to seven days) after the rupture, and death was, therefore, less sudden and unexpected.

The clinical importance of this study seems obvious. Extra precautionary measures should be taken to keep the patient as quiet as possible between the third and sixteenth days after the first attack of coronary thrombosis. This is especially important when the blood pressure remains above 140/90 mm. Hg.

SUMMARY

1. In a series of 25,000 autopsies at the Los Angeles County Hospital between July, 1924, and August, 1941, there were 865 hearts which contained unhealed infarcts caused by coronary disease.

2. Among these were 72 instances of spontaneous rupture through an area of ventricular infarction; 50 (70 per cent) were on the anterior surface of the heart. In 13 instances the rupture was through the interventricular septum.

3. Scarring was present in 58.4 per cent of the unruptured hearts and in only 26.3 per cent of the ruptured hearts.

4. In the ruptured hearts the infarcts tended to be smaller, more completely necrotic, and more heavily infiltrated with polymorphonuclear leucocytes.

5. Of 100 patients who had nonfatal myocardial infarction, 23 (23 per cent) had a blood pressure of 140/90 or above. The average blood pressure was 125/78.

6. Of 657 patients who had myocardial infarction that terminated fatally without rupture, 210 (32 per cent) had a blood pressure of 140/90 or above. The average was 128/81.

7. In 62 patients who died as a result of cardiac rupture, the blood pressure was 140/90 or above in 39 (63 per cent). The average was 148/93.

8. The average calculated time between infarction and rupture was 7.4 days. Ninety-eight per cent occurred on or before the sixteenth day after infarction. Seventy-eight per cent occurred between the third and twelfth days.

9. Among 368 patients with heart weights of 400 grams or more and a blood pressure of less than 140/90 after infarction, only 4 per cent had cardiac rupture.

10. Rupture of the heart occurred in 25 per cent of the 28 patients whose hearts weighed less than 400 grams and whose blood pressures were 140/90 or above after myocardial infarction.

11. In the first 12,500 autopsies in this series, done between 1924 and 1935, 266 instances of myocardial infarction and 23 (8.6 per cent) ruptures were observed. In the second half, done between 1935 and 1941, myocardial infarcts were present in 599 cases and ruptures in 49 (8.2 per cent).

CONCLUSIONS

The following conclusions regarding spontaneous rupture of the heart through an area of myocardial infarction appear justifiable from our data:

1. The degree of softening of the myocardium and the height of the intraventricular pressure are the determining factors in relation to cardiac rupture.

2. Patients who have hypertension which persists after infarction are three times more likely to develop cardiac rupture than those who have normal or subnormal blood pressures.

3. Hearts of normal weight in patients whose hypertension persists after infarction are most likely to rupture.

4. Hypertrophied hearts in patients who have a normal or low blood pressure after infarction are least likely to rupture.

5. If scarring is present in the myocardium, the likelihood of rupture is only one-fourth as great as in unscarred hearts.

6. Interventricular septal ruptures are caused by the same factors that lead to other ventricular ruptures. These patients live longer after rupture, and the diagnosis can be made clinically without great difficulty.

7. Extra precautionary clinical care, to prevent rupture, should be given patients whose blood pressure remains elevated after coronary thrombosis.

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THE EFFECTS OF REPEATED ADMINISTRATION OF LANATOSIDE C ON THE MYOCARDIUM OF THE DOG

HAROLD ROSENBLUM, M.D., GERSON BISKIND, M.D., AND H. E. KRUGER
SAN FRANCISCO, CALIF.

INTRODUCTION

THE ability of digitalis substances to produce changes in the myocardium of the experimental animal has been studied by several investigators.¹ After the administration of sublethal or lethal doses of preparations of digitalis purpurea, digitoxin, and strophanthin to various species, but chiefly to cats and dogs, microscopic examination of the heart muscle has disclosed areas of focal necrosis, cellular infiltration, interstitial edema and fibrosis, and hyaline degeneration. These changes have been found most commonly in subendocardial areas, especially in the ventricular musculature.

The effect on the dog's myocardium of lanatoside C, a crystalline derivative of digitalis lanata, has been studied by Fahr and LaDue,² and by LaDue.³ The first² of these reports dealt with several dogs, but apparently in only one of them was intravenous administration employed. Examination of the myocardium yielded negative results. LaDue studied the effects of toxic and lethal intravenous doses of lanatoside C in a series of nine dogs. In each animal, marked constitutional effects were produced, including anorexia, emesis, and weight loss. With the exception of two dogs, no experiment was carried beyond eight days. In each case, myocardial damage was found by microscopic examination, and "electrocardiographic changes" were "present."³ In a more recent report, LaDue confirmed these conclusions and reported that the simultaneous subcutaneous administration of atropine to dogs which were receiving daily intravenous injections of lanatoside C resulted in a markedly increased survival time for the animals.¹²

PROBLEM AND METHOD

Recent appraisals of the clinical usefulness of lanatoside C, especially its relatively low toxicity² and the rapid dissipation of its lethal effect on animals,⁴ prompted us to study the effects of long-continued administration of this substance on the dog's heart, excluding as far as possible the factors of vomiting, malnutrition, and depletion. The dog has been shown to be a reliable animal for the assay of digitalis substances, and exhibits a smaller standard deviation to toxic and lethal dosage than does the cat.⁴

Kaplan and Visscher⁶ ascertained that the M. L. D. of lanatoside C by intravenous injection is 0.36 mg. per kg. when no anesthetic is used. They found that the majority of dogs vomited when between 20 per cent and 30 per cent of the M. L. D. was injected, and that, in all cases, vomiting occurred when 30 per cent to 36 per cent of the M. L. D. was given.

From the Harold Brunn Institute for Cardio-Vascular Research, and the Department of Pathology, Mount Zion Hospital, San Francisco.

This study was supported by a grant from the Sandoz Chemical Works, Inc., which also supplied quantities of lanatoside C (Cedilanid, Sandoz) and of digitoxin.

Received for publication April 10, 1942.

Thirty per cent of the M. L. D., accordingly, was selected for both lanatoside C and digitoxin as the dose for study in these experiments, with the hope that it would be possible to maintain at least some of the animals over a substantial period of time while toxic doses were being given.

Normal adult male dogs were used. The animals were weighed and were injected intravenously three times a week. The dosage, of course, was determined by the current weight. Vomiting and salivation were constant reactions to each injection, and followed the injection within a few minutes. Injections were given in the mornings and feedings in the late afternoon, by which time appetite had often been regained. Muscular weakness, diarrhea, tachycardia, and ectopic beats were observed in some of the animals. Other animals appeared to remain unaffected, except for the salivation and vomiting immediately after the injection. Several experiments were terminated by the spontaneous death of the animals, and others by sacrificing the animals (by bleeding) after varying periods of administration. The diet consisted of a "complete" proprietary food mixture.

Electrocardiographic changes as a result of giving lanatoside C have been found in dogs by LaDue.³ Others^{2,7} have described digitalis-like effects of this drug on the electrocardiogram in the human being. Electrocardiograms were made on some of our animals before and during the administration of the drugs, but changes caused by positional influences dominated the records to such an extent that they were not considered suitable for the interpretation of digitalis effects.

Lanatoside C, in common with other digitalis preparations, has characteristics of potency which must be expressed differently for different methods of assay,⁸ and in our experiments, therefore, dosage is expressed only in terms of weight.

Methodical sectioning of the myocardium, according to the method of Hu, et al.,¹⁻⁴ was employed.

LANATOSIDE C

Eight dogs were given 0.3 M.L.D. of lanatoside C; that is, 0.108 mg. per kg., by intravenous injection, for periods ranging from twenty-one to ninety-four days.

Of the eight dogs, two (4, 47) showed appreciable changes in one section only. Three dogs (95, 99, 25) showed slight abnormalities in one or two sections, and two were negative throughout (96, 98), as shown in Table I. Four of the eight animals were sacrificed at intervals varying from thirty-eight to ninety-four days. The remaining four, which were found dead, had received lanatoside C for twenty-one to eighty-four days. No animal was included in which post-mortem changes made microscopic examination difficult.

Fig. 1 shows a typical area of necrotic muscle (Section 4-2), rather sharply outlined with fine proliferation of fibroblasts and small capillaries (early granulation tissue). There are remnants of muscle fibers, and the cellular arrangement is mainly mononuclear. This section was taken from the posterior portion of the left ventricular wall of a dog which had received twelve injections of lanatoside C over a period of four weeks.

Fig. 2 shows a section of normal myocardium which was typical of the lack of abnormality in all sections from a dog (38) which had received forty injections over a period of ninety-four days.

Table I shows the weight changes. Extreme loss of weight occurred in only one dog; it suffered from distemper as a terminal illness (96),

TABLE I

DRUG USED AND DOSE	DOG NO.	WEIGHT AT BEGINNING OF EXPERIMENT, (AND NET CHANGE) KG.	REGIONS OF MICROSCOPIC STUDY* (SECTIONS)						NO. OF INJECTIONS	DURATION OF EXPERIMENT
			L.V.A.	L.V.P.	L.V.L.	V.S.	R.V.	R.A.	L.A.	
Lanatoside C 0.108 mg/kg. (0.3 M. L. D.)	95	9.0 (-0.9)	0	0	0	+	0	0	0	15 5½ wks. (sacrificed)
	96	9.5 (-5.4)	0	0	0	0	0	0	0	7 7 wks. (died; distemper, terminally)
	99	10.1 (-0.1)	0	0	0	+	0	+	0	31 84 days (sacrificed)
	4	17.3 (-2.7)	0	++	0	+	0	+	0	12 4 wks. (found dead)
	25	11.4 (-2.3)	0	0	+	0	0	0	0	9 21 days (found dead)
	38	13.2 (-0.9)	0	0	0	0	0	0	0	40 94 days (sacrificed)
	46	11.4 (+0.9)	0	++	0	0	0	0	0	40 92 days (sacrificed)
	47	13.6 (-1.8)	0	++	0	0	+	0	0	8 18 days (found dead)
Digitoxin 0.15 mg/kg. (0.3 M. L. D.)	97	21.8 (-0.4)	+	+	++	0	0	0	0	7 4 wks. (found dead)
	100	11.8 (-1.8)	0	0	++	0	0	+	+	12 6 wks. (sacrificed)**

0 = normal myocardium; + and ++ = slight and moderate myocardial changes, as described in text.

*L.V.A. = Anterior portion left ventricle; including anterior papillary muscle.

L.V.P. = Posterior portion left ventricle; including posterior papillary muscle.

L.V.L. = Lateral left ventricular wall.

V.S. = Anterior portion of interventricular septum.

R.V. = Anterior right ventricular wall.

R.A. = Right auricular wall, including appendage.

L.A. = Left auricular wall, including appendage.

**Animals were sacrificed by bleeding.

and showed no myocardial abnormality. In the remaining animals, the change of weight varied from a moderate loss to a slight gain.



Fig. 1.—Dog No. 4, Section 2. From posterior portion of the left ventricle, showing focal necrosis, mononuclear infiltration, and early granulation tissue; from a dog which had received twelve injections (0.3 M. L. D. each) of lanatoside C in a period of four weeks.



Fig. 2.—Dog No. 38, Section 2. From posterior portion of the left ventricle, showing normal myocardium; from a dog which had received forty injections (0.3 M. L. D. each) of lanatoside C in a period of ninety-four days.

DIGITOXIN

The M. L. D. of digitoxin for dogs has been ascertained⁹ and the effect of its injection on the heart muscle has been fairly well standardized.¹ We attempted to compare its effect with that of lanatoside C by using comparable doses of digitoxin, i.e., 0.3 M. L. D. in a parallel series. The relative unavailability of this substance at the present time, however, permitted its use in only two dogs. A review of the work of Hu, et al.,^{1-d} discloses the usual pathologic changes which follow the administration of digitoxin to dogs when a technique rather similar to ours is employed.

Of our two animals which received digitoxin, one died after seven injections, and the other was sacrificed after twelve injections. In each case, the dose was 0.150 mg. per kg. of body weight. Table I shows the histopathologic changes in the myocardium of each. These changes consisted of subendocardial necrosis, with mononuclear and polymorphonuclear infiltration, as described by Hu, et al.^{1-d}

Table I shows that there was no marked loss of weight in either animal.

DISCUSSION

Table I shows that, in general, when the total nutrition of the animals was maintained in good or fair condition, the pathologic changes in the myocardium were not extensive, especially in the animals to which lanatoside C had been administered. This was true even in dogs which had received toxic doses of the drug over periods as long as ninety-four days. In fact, the dog which was maintained for the longest time showed no abnormalities in the heart muscle. The rapid dissipation of the lethal effect of large doses of lanatoside C in cats in comparison with other digitalis glycosides has been measured by DeGraff and Lehman.⁴

No relationship could be established between the histologic changes in the myocardium and the spontaneous death of an animal. Extracardial lesions (cerebral, suprarenal, hepatic, and renal), as described by Hueper and Ichniowski,¹⁰ may play an important part in causing death after digitoxin administration. These authors believed that some of these dogs showed no myocardial change. Also, no relationship could be found between the number of injections and the pathologic changes. As noted by Hu, et al.,^{1-d} the lesions tend to occur in the ventricles, especially the left. In our animals, no special disease of the coronary arteries or of the Purkinje tissues was found. The changes which have been described have not been seen in the hearts of normal dogs.^{1-d} The mechanism of the production of these lesions is not clearly understood. They may be the direct result of toxic action of the drug on the muscle fibers, or of foci of myocardial ischemia as a result of insufficiency of coronary flow caused by increased myocardial tone. However, moderate doses of lanatoside C or other digitalis bodies do not restrict coronary flow, as measured by the thermostromuhr, in dogs.¹¹

CONCLUSIONS

1. Repeated toxic doses of lanatoside C and of digitoxin were given intravenously to dogs. The attempt was made (by spacing the injections and by the use of an adequate diet) to interfere as little as possible with the nutrition of the animals.

2. Focal myocardial necrosis was found in each of two dogs which had received digitoxin, and to a relatively lesser extent in six of eight dogs which had been given lanatoside C; the two remaining dogs showed no change in the myocardium.

3. No relationship could be established between the clinical condition of the animals and the myocardial changes.

We wish to thank Wilfred Chew for his technical assistance in this study.

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SYPHILITIC CORONARY STENOSIS, WITH MYOCARDIAL INFARCTION

GEORGE E. BURCH, M.D., AND TRAVIS WINSOR, M.D.
NEW ORLEANS, LA.

IT IS generally conceded that syphilis of the cardiovascular system affects the heart and contiguous structures in at least six ways. There may be (a) aortitis, with inflammation of the adventitia, media, and intima; (b) aortic aneurysm, either diffuse or saccular; (c) valvulitis or inflammation of the aortic ring, producing regurgitation; (d) coronary arteritis, producing stenosis of the ostia of the arteries; (e) myocarditis, producing either diffuse or gummatous lesions; and (f) syphilitic coronary arteritis, resulting in myocardial infarction. It is our purpose to discuss the latter condition as found at Charity Hospital among 6,225 routine, consecutive autopsies, performed between January 1, 1937, and January 1, 1942; and to record a specific instance of this condition.

STATISTICS

During the past five years, 287,257 patients, about half of whom were colored, entered the wards of Charity Hospital; 21,642 (7.5 per cent) of these were discharged with a clinical diagnosis of heart disease. Of this group with heart disease, 326 (1.5 per cent) had myocardial infarction resulting from a variety of causes, and of these only 3 (0.9 per cent) had myocardial infarction secondary to syphilitic coronary stenosis. Among the 6,225 consecutive routine autopsies, there were 4,610 (74 per cent) with a post-mortem diagnosis of heart disease, in 185 (4.0 per cent) of which myocardial disease of various kinds caused death; in only three (1.6 per cent) of these was infarction produced by syphilitic coronary narrowing; therefore, myocardial infarction as a result of syphilis is rare.

Of the total number of autopsies, in 193 (3.1 per cent) there was syphilitic aortitis. Forty (20.7 per cent) of the patients with aortitis had narrowing of one or both coronary arteries as a result of syphilitic infection of the aorta, and only 3 (7.5 per cent) of these had myocardial infarction secondary to the stenosis. Of the 193 patients with syphilitic aortitis, only 3 (1.5 per cent) died of myocardial disease caused by coronary narrowing. The incidence of aortitis in routine autopsies, as reported by other observers, varies from 2.7 per cent to 7.0 per cent,^{1, 2} whereas that of aortitis with syphilitic coronary narrowing varies between 8.4 per cent and 35.0 per cent.^{3, 4} Figures from selected sources are shown in Table I.

From the Department of Medicine, School of Medicine, Tulane University of Louisiana, and Charity Hospital of Louisiana.

Received for publication May 7, 1942.

TABLE I

THE INCIDENCE OF (1) SYPHILITIC AORTITIS AND (2) SYPHILITIC AORTITIS WITH SOME DEGREE OF STENOSIS OF THE CORONARY ORIFICES, FROM VARIOUS REPORTS OF AUTOPSIES

SYPHILITIC AORTITIS		SYPHILITIC AORTITIS WITH CORONARY STENOSIS	
AUTHOR	PER CENT	AUTHOR	PER CENT
Cornia ¹	2.7	Carr ³	8.4
Burch and Winsor	3.1	Reid ⁵	12.8
Reid ⁵	3.2	Martland ⁹	14.9
Symmers ⁶	3.5	Clawson and Bell ¹⁰	19.9
Cowan and Faulds ⁷	6.0	Burch and Winsor	20.7
Pineoffs and Love ⁸	6.9	Saphir ¹¹	31.0
Oberndorfer ²	7.0	Bruenn ¹²	33.1
		Saphir and Scott ⁴	35.0

The relative importance of myocardial infarction in patients with syphilis of the cardiovascular system is shown by the fact that about one-fifth of the patients with syphilitic aortitis have involvement of the coronary ostia, whereas only one or two per cent with syphilitic aortitis have myocardial infarction. Seven or eight per cent of the group with coronary narrowing, however, have myocardial infarction. Only six cases of cardiac infarction from syphilitic coronary stenosis were found in the literature during the past ten years. Bruenn¹² studied 39 autopsies on patients with coronary stenosis and found that three of these had myocardial infarction. Saphir¹¹ described one such case. Briskman¹³ described two patients who probably had myocardial infarction. Norris¹⁴ described three patients with myocardial change, but doubted that coronary occlusion was the etiologic factor.

The average age of the patients in the Charity Hospital series who had syphilitic coronary narrowing was 45 years. The youngest person with this condition was 20, and the oldest, 70. Seventy-five per cent of the 40 patients were between the ages of 30 and 60. This fits in well with the expected time of appearance of cardiovascular syphilis.

Both of the coronary ostia were involved in 29 (72.5 per cent) of the patients who had some degree of stenosis of the coronary orifices. The right alone was involved in 7 (17.5 per cent) and the left in 2 (5.0 per cent). Love and Warner¹⁵ reported 15 autopsy cases of syphilitic coronary stenosis. In 8 (53.3 per cent) of these there was stenosis of both coronary ostia, in 6 (40.0 per cent), stenosis of the right coronary orifice only, and in one (6.6 per cent), narrowing of the left coronary orifice.

The race distribution of the 40 patients with coronary stenosis at Charity Hospital was 6 white and 34 colored, a ratio of about 1 to 6. Of the three with myocardial infarction, all were colored. The sex distribution of the patients was 9 females and 31 males, a ratio of about 1 to 3.5.

The Wassermann reaction was recorded in 27 of the 40 patients with syphilitic coronary stenosis; it was positive in 26 (96.3 per cent). Pincoffs and Love⁸ state that a positive blood Wassermann reaction is a valuable diagnostic sign; the reaction was positive in all of their autopsied patients who had narrowing of the coronary arteries caused by syphilis.

The weight of the heart varied, depending on whether or not there was: (a) aortic regurgitation, (b) hypertension, (c) aortic regurgitation and hypertension combined; (d) syphilitic coronary stenosis, or (e) aortic aneurysm. These variations are shown in Table II.

TABLE II

HEART WEIGHTS (GRAMS) IN FORTY CASES OF SYPHILITIC CORONARY STENOSIS, CORRELATED WITH CERTAIN ASSOCIATED ABNORMAL STATES

PATHOLOGIC STATE	NO. OF CASES	MEAN HT. WT.	MINIMUM HT. WT.	MAXIMUM HT. WT.
1. Aortic regurgitation and essential hypertension	2	798	650	945
2. Essential hypertension	5	634	330	900
3. Aortic regurgitation	20	609	315	945
4. Syphilitic coronary stenosis alone	4	413	220	500
5. Aortic aneurysm	2	288	220	355

Although the number of cases is small, the data tend to indicate that the heaviest hearts were from patients who had a combination of aortic regurgitation and essential hypertension. Either of these conditions alone generally resulted in a marked increase in cardiac weight. The average weight when coronary stenosis was associated with hypertension, aortic regurgitation, or a combination of these conditions, was 680 grams. In two cases, aortic aneurysm did not produce an increase in cardiac weight (average for the two hearts, 288 grams). Coronary stenosis alone, however, was associated with an average heart weight midway between these two figures, namely, 413 grams. These figures agree with those of Bruenn.¹² He found that the heart with syphilitic coronary stenosis was only moderately enlarged (largest, 420 grams) whereas the heart with coronary stenosis associated with aortic regurgitation was greatly enlarged.

The following case illustrates the clinical picture of myocardial infarction caused by syphilitic obstruction of the coronary orifices.

REPORT OF CASE

L. A., a 39-year-old colored woman, married, a shrimp worker, entered the Charity Hospital November 7, 1941, and died November 8, 1941.

The patient had been well until six weeks before entrance, when she first noted pain in the chest and dyspnea which came on suddenly after meals or exertion. The pain was most intense about the lower end of the sternum, and radiated to the left shoulder and down the arm to the level of the elbow. The pain was sudden in onset, vise-like in character, and severe enough to produce crying. It frequently

lasted fifteen to twenty minutes. She had two or three such attacks daily, and they increased in frequency and duration until the day of the admission, at which time she experienced the most excruciating attack she had ever had. At this time she coughed up some blood-tinged sputum.

There was no history of syphilis. On October 12, 1941, her blood Wassermann reaction was positive. An electrocardiogram on the same date showed only left axis deviation.

On entrance her temperature was 99.2° F., her pulse rate, 120 per minute, her respiratory rate, 30 per minute, and her blood pressure, 115/80. She was moderately obese, and was sitting in bed gasping for breath. The pupils were circular, equal, and reacted well to light and accommodation. The heart was moderately enlarged to the left. A soft systolic murmur was heard at the mitral area. The pulmonic second sound was louder than the aortic second sound. Fine moist râles were heard throughout both lungs posteriorly. The liver was palpable four centimeters below the costal margin. Slight edema of the ankles was present.

The patient was treated with digitalis, aminophyllin, oxygen, and hypertonic glucose solution intravenously. She became increasingly dyspneic and edematous, and coughed up some bloody, frothy material. She died suddenly November 8, 1941, after six hours of hospitalization.

Necropsy.—The heart weighed 350 grams. It was dilated and flabby. There was definite evidence of infarction of the major portion of the left ventricle and the lower portion of the interventricular septum. The aortic valves were slightly thickened and the commissures were negligibly widened. Both coronary ostia were markedly narrowed at the aortic wall, but beyond this point the vessels were widely patent. No emboli were found. The circumference of the aortic ring was not enlarged. The aorta showed typical oak-bark wrinkling at the root. Circumscribed, elevated, edematous plaques were seen in the first part of the aorta and in the sinuses of Valsalva.

Microscopically, the cardiac muscle was edematous, and many of the fibers showed hyalinization and necrosis. The endocardium was thickened by the presence of fibrin, round cells, and some polymorphonuclear cells. The aorta was the seat of intimal thickening and infiltration with lymphocytic cells. The vasa vasorum showed intimal thickening and perivascular collars. Lymphocytic infiltration was most marked in the tissue between the adventitia and media.

DISCUSSION

The history of severe precordial pain, referred to the inner aspect of the left arm, in a middle-aged colored person with a positive Wassermann reaction and no arteriosclerosis or hypertension suggests the possibility of syphilitic coronary narrowing. This patient presented such a picture. Bruenn¹² states that precordial pain is the presenting complaint of the majority of patients with the syphilitic coronary syndrome; twenty-three of his thirty-five patients with coronary stenosis had anginal pain. It must be borne in mind, however, that many patients with coronary stenosis, and even those with complete closure of both coronary ostia (vide infra), may have no precordial pain of any kind. On the other hand, syphilitic aortitis, with or without aneurysm or aortic insufficiency, and numerous nonsyphilitic states may produce precordial pain which is indistinguishable from that characteristically produced by syphilitic coronary stenosis. The race and age of the patient¹⁶ suggested the possibility of syphilis as a cause of coronary

stenosis. The positive Wassermann reaction was highly compatible with syphilitic coronary stenosis, as pointed out by Pincoffs and Love⁸ and as shown by the records from Charity Hospital. The size of the heart was in keeping with syphilitic coronary stenosis. The short course of her illness (only six weeks from the onset of the precordial pain), the typical pain of coronary occlusion, the lack of response to treatment, the history of infrequent previous hospital admissions, and the fact that the patient grew worse rapidly fitted in well with the diagnosis of syphilitic coronary stenosis with myocardial infarction.

PATHOLOGY

A vascular phenomenon underlies many of the pathologic changes in both the early and late stages of syphilitic disease. Any organ of the body may be involved, and numerous dissimilar lesions are frequently produced. Coronary occlusion, aortic aneurysm, cerebral hemorrhage, primary chancre, gastric ulcer, and necrosis of gummata are secondary to vascular changes, and all present the picture of a productive obliterating arteritis which involves all three coats of the arteries.^{17, 18} Such lesions may obstruct the coronary, carotid, innominate, or spinal arterial ostia, or they may weaken their walls to produce aneurysm or dilatation.¹⁹

Microscopically, the adventitia of the coronaries shows an accumulation of small round cells, particularly about the vasa vasorum. Moritz²⁰ states that the inflammation usually begins about the vasa vasorum in the adventitia of the vessel. This process penetrates the media and intima by extension of the inflammation along the smaller vessels.¹⁹ The media becomes infiltrated with lymphocytic and small round cells which replace the healthy muscle and elastic tissue. The intima is greatly thickened as a result of the formation of succulent vascular inflammatory plaques which occlude the ostia of the coronary arteries at the point where they pass through the aortic wall. Such exudative, edematous lesions may encircle the aortic root, forming the so-called "girdle of Venus."¹⁸ When the coronary ostia are involved, usually only the first 30 millimeters of the artery are affected, and beyond this point the vessel widens and remains patent throughout its entire length. Involvement of the distal branches is rare.^{9, 10, 20-26} Cormia,¹ however, states that the distal portions of the coronary arteries are involved in 23 per cent of the cases of narrowing of the coronary ostia caused by syphilitic aortitis.

The high incidence of coronary stenosis is due, in large part, to the location of the coronary ostia in the aortic wall, as well as to the distribution of the blood supply of the coronary ostia and aortic root. The locations of the coronary orifices are not constant. Ordinarily, they are within the sinuses of Valsalva, but this is by no means invariable. Occasionally they are found one or two centimeters above the sinuses, in which case they are more easily involved in the syphilitic

infiltration at the root of the aorta.²⁷ Wearn²⁸ states that the high incidence of ostial involvement is due to the fact that a branch of the coronary artery supplies the first part of the aorta in the region where aortitis is most common.

The time of appearance of syphilitic coronary stenosis in cases of syphilitic aortitis is often early in the course of the disease, for stenosis is sometimes found in an aorta which is almost free from syphilitic involvement.²⁰

It is frequently difficult to distinguish between syphilitic and arteriosclerotic coronary disease, for, in either case, plaques are formed which may be similar in appearance and location. Fatty changes and calcification may occur in either condition. In syphilis the inflammatory process extends from the adventitia to the intima, and a fibrotic exudative change takes place within all the vascular coats. Fatty change, with cholesterolization and calcification of all arterial structures, may result secondarily. In arteriosclerosis the fatty change takes place early in the intima, and a superficial fibroblastic change, which penetrates no deeper than the intima, occurs later. Frequently, both a syphilitic and arteriosclerotic process are present.¹³ Leary¹⁸ states that arteriosclerotic changes are frequently engrafted upon old syphilitic lesions, and, as these regress, the arteriosclerotic changes become more prominent. There are, however, certain abnormalities in the cardiovascular system which help to distinguish between syphilitic and arteriosclerotic coronary disease. In syphilis, the coronary arteries show thickening of all three coats, longitudinal wrinkling of the intima, edematous plaques about the ostia of the arteries, and patency of the terminal portion of the artery. There are perivascular round cell infiltration and, more rarely, gummata about the coronary ostia. In arteriosclerosis there are no Longcope plaques, nor is there wrinkling of the intima. The coronaries are tortuous, hard, and brittle, and contain firm yellow plaques which extend throughout the length of the artery.²² Glistening fibrous tissue is sometimes found in the left ventricular musculature.

The myocardial change which results from coronary arteriosclerosis and syphilitic coronary stenosis may be similar. Fibrosis and lymphocytic infiltration of the myocardium will be found if cardiac ischemia has been present. If a sudden coronary stenosis had taken place, myocardial infarction would be present provided death had not occurred too suddenly. In patients with syphilitic coronary stenosis there is no essential relationship between coronary closure and myocardial change. This is because of the insidious involvement of the arteries and the rich collateral circulation which develops. Briskman¹³ described four patients with syphilitic coronary stenosis who died suddenly. At necropsy two showed atrophy of the myocardium and one myocardial fibrosis, and, in one, the myocardium was unaltered.

The collateral circulation which results from slow coronary occlusion is extensive.^{20, 30} Wearn, et al.,³¹ have shown by injection methods that

the artero-luminal, artero-sinusoidal and Thebesian vessels, all of which run between the coronary vessels and chambers of the heart, are probably active in such cases. Pratt³² was able to keep a cat heart beating for one hour by perfusing blood through the auricles and ventricles. This seems to indicate that the cardiac musculature can be nourished by blood passing through the chambers of the heart, and is not entirely dependent upon blood entering through the coronary vessels. In syphilitic coronary stenosis the vessel is usually patent beyond the obstruction at its orifice. This suggests that blood flows through these vessels, although the coronary ostia may be completely closed. Leary¹⁸ states that collateral vessels develop through the pericardial, bronchial, and aortic vasa vasorum, and contribute to the nutrition of the heart when coronary stenosis exists.

DIAGNOSIS

Syphilitic coronary stenosis with or without varying degrees of myocardial infarction is frequently suspected clinically, but the diagnosis may be impossible to prove. In general, anginal pain, a moderately enlarged heart, and a positive Wassermann reaction in a young male Negro, who responds poorly to digitalis or antisyphilitic drugs and grows worse rapidly, should indicate the presence of syphilitic coronary stenosis. If, in addition, there are shock, hypotension, muffled heart tones, a pericardial friction rub, leucocytosis, and an elevated sedimentation rate, myocardial infarction secondary to syphilitic coronary narrowing should be considered. In such cases, however, death may occur so rapidly that these typical signs of myocardial infarction do not have time to develop.

Syphilitic coronary stenosis is found in relatively young persons. Bruenn¹² states that the average age is 34 years. At Charity Hospital the age of the patients varied between 30 and 60. The patients with syphilitic aortitis reported by Longcope¹⁹ were in a similar age group, i.e., between 30 and 50. Patients with arteriosclerotic coronary disease are likely to be older.

Syphilitic coronary stenosis is frequently associated with aortic regurgitation. This is important because patients with the latter condition should be suspected of having involvement of their coronary arteries. Eighty-seven and one-tenth per cent of Bruenn's¹² patients with syphilitic coronary stenosis also had involvement of the aortic valves, and 76 per cent of the patients at Charity Hospital with coronary stenosis had definite aortic regurgitation. When aortic insufficiency is found in a young, white person it is likely to be the result of rheumatic fever, which only rarely involves the coronary arteries, whereas aortic regurgitation in a young, colored person is more likely to be syphilitic. At Charity Hospital, the coronary arteries showed syphilitic involvement six times more frequently in the colored race than in the white.

The pain caused by syphilitic coronary stenosis frequently simulates angina pectoris. It develops suddenly, is viselike in character, and tends to radiate from the precordium to the arm, neck, back, or epigastrium. It generally lasts from a few seconds to a few minutes and is precipitated by eating or exercise. Pinecoffs and Love⁸ found that 86.6 per cent of their patients with syphilitic coronary stenosis had typical angina. They state that anginal pain is rare in patients with uncomplicated aortitis, but is common in those with syphilitic coronary stenosis. Anginal pain may, however, be present with other forms of cardiovascular disease. If angina occurs in a patient under 40 years of age with a positive Wassermann reaction, the pain is probably syphilitic in origin; if the patient is over 40, it is probably caused by coronary arteriosclerosis.⁸ Willius³³ states that angina of over ten minutes' duration is likely to be caused by organic coronary change, and is indicative of syphilitic stenosis if the patient is a young Negro. Longcope¹⁹ states that the pain of aortitis is produced by inflammation at the root of the aorta or by bronchospasm. This type of pain may be confused with the anginal pain caused by coronary involvement. Typically, the pain associated with aortic regurgitation or aortic aneurysm does not tend to radiate. It is present as a constant, viselike, substernal oppression. On the other hand, there may be extensive involvement of the root of the aorta or complete stenosis of both coronary ostia without any pain whatsoever.³⁴ Albutt³⁴ states that a man may be fairly comfortable with both coronary ostia completely occluded. Kokita²⁷ reported a patient with acute congestive heart failure without angina pectoris who had complete occlusion of one coronary orifice.

The mechanism of the production of the pain is not clear. Leary³⁵ states that coronary spasm is a factor in producing angina and sudden death. Lewis³⁶ and Katz³⁷ state that myocardial ischemia produces circulatory metabolites which are responsible for the pain. Norris³⁸ believes that the pain is caused by inflammation of the pericoronary nerves. These factors are probably important, but they do not explain all clinical or experimental observations.

Cardiac enlargement, we found, is only moderate in cases of uncomplicated syphilitic coronary narrowing. This is in agreement with Bruenn,¹² who states that the largest of thirty-nine hearts which were the seat of coronary stenosis weighed 420 grams; the average was 370. In the Charity Hospital study the greatest heart weight with uncomplicated coronary narrowing was 500 grams, and the average was 413 grams. The cause of this moderate hypertrophy is not clear. It has been suggested that myocardial ischemia tends to prevent cardiac hypertrophy. This explanation is inadequate.

Patients with coronary stenosis and aortic regurgitation, coronary stenosis and essential hypertension, or coronary stenosis, aortic regurgitation, and essential hypertension had very heavy hearts; the average was 680 grams, and the greatest, 945 grams. The largest hearts are

generally produced by rheumatic heart disease, arteriosclerosis, hypertension, and aortic regurgitation. These may weigh nearly 1,000 grams.³⁸ Such cardiac enlargement is not usually caused by uncomplicated coronary stenosis. On the other hand, if coronary stenosis is associated with aortic aneurysm, the weight is not increased markedly. In this group the average weight was 288 grams, and the greatest weight was 355 grams.

The blood Wassermann reaction, if it is positive, is a valuable suggestive sign of cardiovascular syphilis, and more particularly of coronary stenosis. Scott³⁹ states that 10 per cent of patients with aortitis have a negative Wassermann reaction. Longcope¹⁹ found positive Wassermann reactions in 75 per cent of his patients with cardiovascular syphilis, and Warr¹⁶ found positive reactions in 74 per cent. Pincoffs and Love⁸ state that the complement fixation test was positive in all of their patients with syphilitic coronary stenosis. At Charity Hospital, 96.3 per cent of twenty-six patients with coronary stenosis had a positive Wassermann reaction in spite of the fact that most of these patients had had some antisyphilitic treatment.

The electrocardiogram usually gives little evidence of syphilitic coronary involvement. Although little is known concerning the electrocardiographic changes secondary to syphilitic coronary narrowing, one would expect them to be similar to those which occur with myocardial ischemia or myocardial infarction resulting from other causes. Bruenn¹² reported left axis deviation and abnormal T waves in a significant number of patients with coronary stenosis and aortic regurgitation. Juster and Pardee⁴⁰ reported abnormal T waves in 85 per cent of thirty-five patients with syphilitic aortitis. Willius³³ states that a negative T_1 and T_2 are common in cases of obliterative arterial disease of the left coronary artery, and that this indicates myofibrosis or a healed or healing myocardial infarct. Moritz²⁰ reported three patients with coronary arteritis who died suddenly; all had normal electrocardiograms and two had angina, but at necropsy neither showed any evidence of myocardial infarction. The three patients with myocardial infarction at Charity Hospital died so quickly that electrocardiograms could not be taken.

It is often difficult to differentiate syphilitic coronary stenosis from conditions which resemble it. (1) In simple aortitis, precordial pain is usually absent, the T waves in the electrocardiogram are not abnormal, and the aortic second sound is usually not tympanitic. (2) In aortic aneurysm, a fusiform or saccular dilatation of the aorta may be seen roentgenographically or fluoroscopically, and the aortic second sound usually is tympanitic. Diadrast may be used to outline the aortic enlargement, and pain, if present, is usually constant and nonradiating. Pressure phenomena may complicate the picture. (3) In aortic insufficiency, a large, forcefully beating heart and prominent peripheral signs are observable. The pain is usually constant, but may be anginal in character. The response to treatment is poor, and the patient is

usually admitted to the hospital only once. The life expectancy is somewhat more than a year from the onset of symptoms. Sudden death may ensue. These patients have a high incidence of concomitant coronary stenosis. (4) Pure coronary stenosis shows itself clinically as angina, dyspnea on exertion, or paroxysmal nocturnal dyspnea. The response to treatment is poor, and the life expectancy is approximately three months after the onset of symptoms. The patient is usually under 40 years of age, and a positive Wassermann reaction is common. A relatively slow death, with congestive heart failure, is the rule; however, sudden death from anginal failure may occur. The heart is usually only moderately enlarged. When the myocardium becomes rapidly involved as a result of coronary stenosis, there may be a history of sudden, agonizing, precordial pain which lasts for more than ten minutes. Fever, leucocytosis, an elevated sedimentation rate, electrocardiographic changes, a friction rub, and an enlarging heart indicate the presence of myocardial infarction. Other signs of myocardial infarction are a low systolic blood pressure, a diffuse apical thrust, muffled heart tones, dyspnea, edema, orthopnea, pulmonary hypertension, paroxysmal nocturnal dyspnea, gallop rhythm, and heart block or Stokes-Adams attacks. Auricular fibrillation is unusual.

PROGNOSIS

Patients with cardiovascular syphilis die more frequently from their cardiac disease than from intercurrent illnesses. Cormia¹ states that, of 199 patients with cardiovascular syphilis, all but six died of heart disease. Sudden death has been defined as that which occurs within six hours from the onset of symptoms. In cardiovascular syphilis, death is usually sudden and may be caused by a variety of conditions: (1) A ruptured aortic aneurysm may discharge its contents externally, into the pleural space, trachea, bronchi, esophagus, mediastinum, or the pulmonary artery. Death is usually sudden except in the latter case, in which the patient may live for months. (2) A dissecting aneurysm, beginning with rupture of an aortic vasa vasorum and dissection of blood into the pericardial space, may produce cardiac tamponade. Death is usually sudden, but it may be slow if the hemopericardium develops slowly and the pericardial membrane stretches greatly. (3) Congestive heart failure caused by aortic regurgitation or ruptured aortic valve cusps may occur. Death is sometimes sudden, but it is more usually slow and is caused by the low diastolic blood pressure, with poor coronary circulation. (4) Congestive heart failure secondary to myocardial syphilis usually causes death within two or three months. (5) Coronary embolism resulting from thrombosis in the area of aortitis causes sudden death.⁴¹ (6) A Herxheimer reaction produces death in a few hours. (7) Lastly, coronary stenosis with or without myocardial infarction may be a cause of death. In the latter group, sudden death may occur, but a rapidly fatal course is more common. Pineoffs and Love⁸ reported

six patients with coronary stenosis who lived an average of 2.3 months after the onset of symptoms. They grew worse rapidly and did not respond to treatment. Bruenn¹² states that the average length of life after cardiac symptoms appear in patients with coronary stenosis is 3.2 months. Patients with coronary stenosis and myocardial infarction are likely to die suddenly. Of the three patients with myocardial infarction caused by syphilitic coronary stenosis in the Charity Hospital series, one was sitting in bed when he developed acute congestive heart failure; he died about six hours later. One patient was kneeling in church when she was struck with precordial pain. She died within the hour in the emergency room at Charity Hospital. The third patient had acute congestive failure when he entered the emergency room and died before he could be admitted to the ward. All three of these hearts showed gross and microscopic evidence of infarction.

SUMMARY

The protocols of 6,225 consecutive autopsies at the Charity Hospital of New Orleans during the past five years were reviewed in order to ascertain the incidence of myocardial infarction secondary to syphilitic coronary stenosis. Three such patients were found. These comprised 1.6 per cent of all cases of myocardial infarction. A review of the literature revealed nine other patients with myocardial infarction caused by syphilis.

The average age of the patients with syphilitic coronary stenosis was forty-five years. Both arteries were involved in the majority of cases. Among the patients with coronary stenosis, the white to colored ratio was about one to six, and the female to male ratio was about one to three and a half. The blood Wassermann reaction was positive in 96.3 per cent of the patients with coronary stenosis. The average weight of the hearts with coronary stenosis alone was 413 grams, whereas patients who had had coronary stenosis and aortic regurgitation, hypertension, or both, had an average heart weight of 680 grams.

A case of myocardial infarction secondary to syphilitic coronary stenosis was described to illustrate the clinical picture.

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CONGENITAL AORTIC AND MITRAL ATRESIA

REPORT OF A CASE AND REVIEW OF THE LITERATURE

ROLAND WALKER, PH.D., AND GUSTAVUS H. KLINCK, JR., M.D.
TROY, N. Y.

REVIEW of the literature shows that complete mitral and aortic atresia is a relatively rare condition. A case in which there were these and associated anomalies led us to study the variants described by others, and to summarize their work in relation to our observations.

CASE REPORT*

The patient, a white female child, five days old, was born spontaneously and was apparently normal, evidencing the usual color, cry, and activity. On the day after birth, it was noted that the child was pale but nursed well. On the second day after birth, the infant had to be urged to nurse. On the third day, there was evidence that it tired very easily while feeding and that its color remained very pale. The child was listless for the greater part of the third day, and, in the evening, when the temperature fell to 97° F., warm blankets were applied. On the fourth day, it was noted that respiration was rapid, shallow, and labored. In addition, cyanosis was present, and the baby continued to be cold. Breast milk was refused. Later in the day the cyanosis became marked and the heartbeat weak. While being lifted from the crib for a blood cell count, the child ceased breathing. Artificial respiration and stimulants were given to no avail.

Mother's Record.—The mother was twenty-four years of age and had been delivered of a normal, full-term child three years previously. At that time, complement-fixation tests for syphilis on the maternal and cord blood were negative. There is nothing to show that complement-fixation tests were done on the mother and child at the time of delivery of the infant who presented the cardiac anomaly under discussion. There was no history of abortion. Recovery from delivery was uneventful.

Autopsy.—Gross examination showed an apparently normally developed and well-nourished child, measuring 47 cm. in length. Slight general lividity and cyanosis of the nail beds were noted. The subcutaneous tissues were normally moist. The peritoneal cavity contained about 25 c.c. of clear yellow fluid that was slightly viscid. The thymus gland measured 3.5 × 3.5 × 1 cm. and presented nothing unusual.

The heart appeared to be enlarged but was not weighed because it was left attached to the lungs and great vessels. In situ, the organ measured 5 cm. in its greatest transverse diameter and 4.5 cm. in its greatest vertical diameter. The right atrium was much enlarged, whereas the left was reduced in size. The ventricular mass had no groove indicating subdivision into right and left portions, but the pattern of the coronary vessels (confirmed by dissection) showed that the right ventricle formed the major portion of the mass, and included the apex, whereas the left ventricular wall consisted of a small patch on the left dorsal side (Fig. 1).

The right and left atria received, respectively, the venae cavae and pulmonary veins in the usual manner. These vessels were of normal size. The interatrial foramen ("foramen ovale," which we think may be a persistent ostium primum) was circular and measured 0.6 cm. in diameter.

Department of Biology, Rensselaer Polytechnic Institute, and the Pathological Laboratory of the Samaritan Hospital.

Received for publication April 15, 1942.

*The authors express their gratitude to Dr. W. B. D. Van Auken, of Troy, N. Y., for the privilege of using his records and for permission to report this case. Samaritan Hospital No. 78296; Autopsy: A-39-49.

The right ventricle was enormous; its walls averaged 0.6 cm. in thickness. The atrioventricular opening was surrounded by a large valve which showed some tendency to be divided into segments. At the upper portion of this chamber, near a point where the pulmonary artery would normally arise, was a large arterial trunk 1.1 cm. in diameter. Near its origin were three well-formed valve leaflets, of the semilunar type, arranged around a ring 3 cm. in circumference.

The left ventricle was merely a small, blind cavity, $1.8 \times 0.7 \times 0.1$ cm., lined by smooth, normal endocardium, in the wall of the right ventricle. The mitral valve and aortic ostium were completely atretic, and the interventricular septum was normal. The mitral valve was represented by a thin imperforate membrane, approximately 0.2 cm. in diameter.

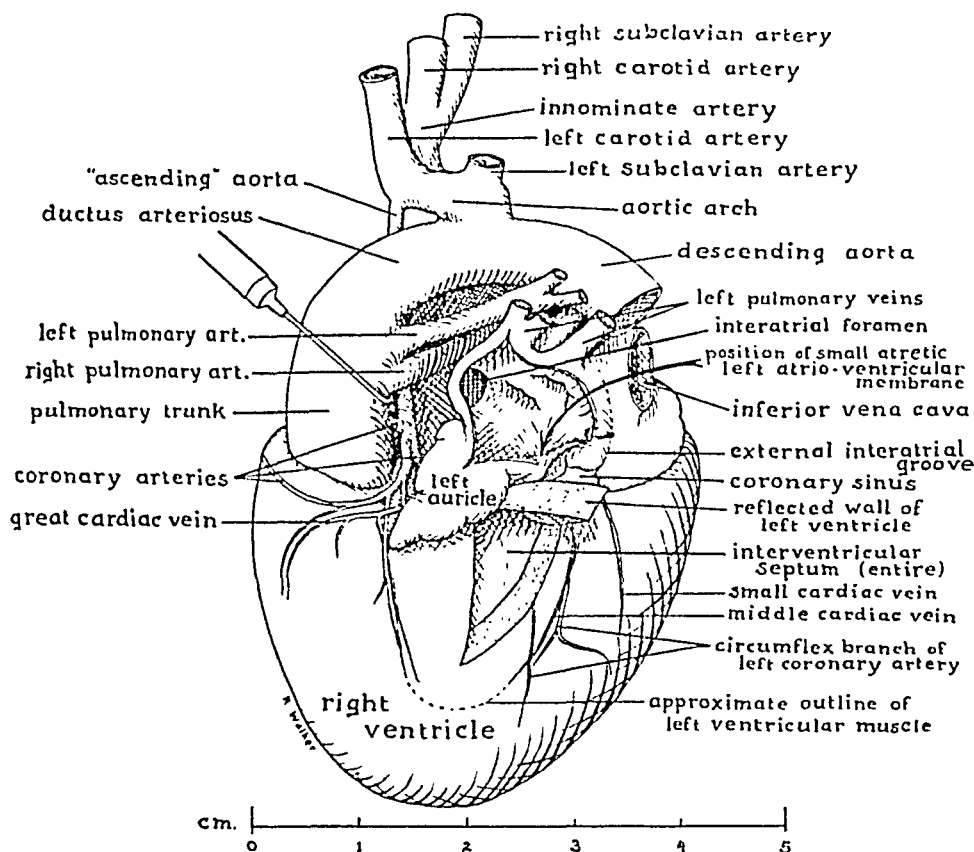


Fig. 1.—Heart viewed from the left.

The great arteries arising from the heart bore the normal fetal morphologic relations but were greatly disproportionate in size. The pulmonary trunk arose from the right ventricle in the usual manner and measured 1.1 cm. in diameter. After giving off right and left pulmonary arteries of normal size, the vessel continued to the left as the ductus arteriosus (0.8 cm. in diameter) which, after giving off a branch, continued as the descending aorta. The branch just mentioned represented the aortic arch, which gave off normal neck vessels as well as a small "ascending aorta," 0.2 cm. in diameter.

The "ascending aorta" terminated in a blind pocket, with no ridges indicating even remnants of semilunar valves. At its lowest point of patency, this rudimentary aorta gave off right and left coronary arteries which had an approximately normal distribution. The blind end, or "root," of the aorta lay, as is normal, directly opposite the commissure between two of the pulmonary cusps. In relation to the interventricular septum, however, it was misplaced, for it lay almost directly above the

right face of the septum. Thus, its wall bulged slightly into the upper corner of the right ventricle, and it was separated by some distance from the blind, functionless left ventricle.

Histologic examination of the major organs showed no remarkable changes. Particular attention was directed to the myocardium of the right and left ventricles, especially in the region of the atretic mitral and aortic valves. As far as we could ascertain, there were no signs indicating old inflammatory disease which might have accounted for atresia of either orifice. The muscle fibers were of normal size. No cellular infiltration was present.

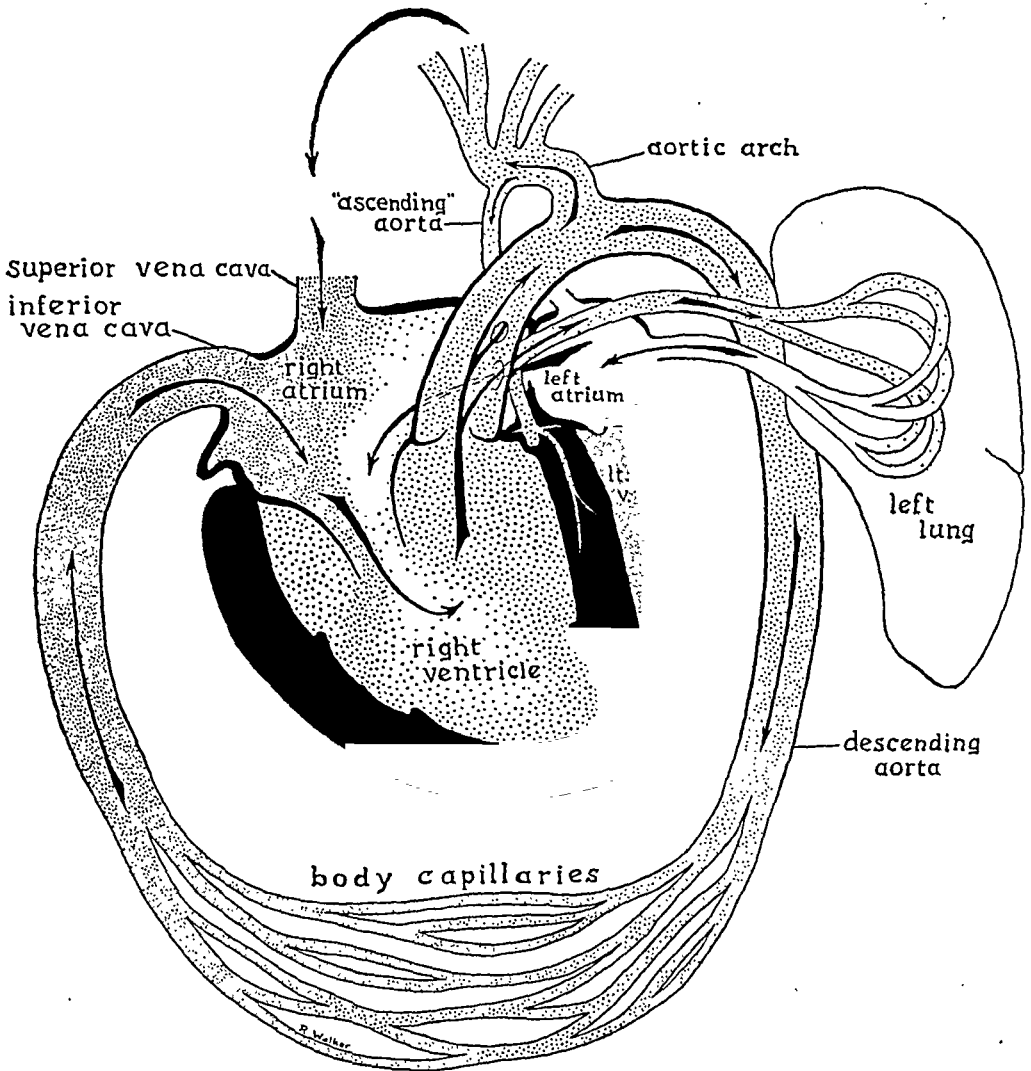


Fig. 2.—Diagram interpreting probable function.

Functionally, the structural conditions implied a complete mixing of pulmonary and systemic venous blood in the right atrium and ventricle, with distribution of equivalent, partly aerated blood to pulmonary, coronary, head, and systemic arteries (Fig. 2).

The morphologic picture consisted of atresia of all openings to the left ventricle, with hypoplasia of the left ventricle and atrium, and of the aorta, together with a wide compensatory defect in the interatrial septum, patency of the ductus arteriosus, and right-sided hyperplasia. The "ascending" aorta carried blood destined only for the coronary arteries, but in a direction opposite normal.

DISCUSSION

Although no exactly similar case has been found in the literature, the above general picture, with variations, has been presented in many cases. However, it is well to delimit the essential points and to show the bearing of the present case on the discussion as to the etiology of similar conditions. We have not attempted to review every pertinent paper, especially in the literature of the past century, but it is hoped that we have considered the most significant work of the last decades.

First, it should be clearly understood that inflammatory mitral stenosis of the adult (Lutembacher's syndrome¹) is not comparable to fetal anomalies of development. With adult mitral stenosis there is sometimes aortic stenosis, as well. Only when there is an associated interatrial defect can the condition progress far, but in such cases there is neither the left-sided hypoplasia nor the patent ductus which are found in developmental anomalies.

Passing mention might be made of congenital pulmonary and tricuspid atresia.^{2, 3} In such cases the conditions are similar to, but reversed from, the aortic and mitral atresias. There are right-sided hypoplasia, patency of the ductus and foramen ovale, and complete mixing of the blood in the enlarged left side. The variation in detail is similar to that in the series to be reviewed below, and a discussion of the etiology would probably be similar, i.e., it is to be expected that any check of flow through the right ventricle at an early stage, whether as the result of inflammatory disease or of misplacement of a septum, and whether the tricuspid or pulmonary valve was primarily involved, would entail the consequences observed.

Again, we would merely note the intermediate cases^{4*, 5} in which aortic atresia or stenosis is associated with transposition of the arteries and right-sided hypoplasia, so that the results are functionally similar to ours. The case of Mills⁶ seems to approximate this condition, although the ambiguity of his description leaves doubt as to whether this heart belongs here or in the main series reviewed later.

Certain reports of cases otherwise similar to ours describe a single ventricle, i.e., either absence of the left ventricle or absence of the inter-ventricular septum. In some cases this may be so, but certain descriptions⁷⁻¹² leave a little doubt as to whether the authors may have overlooked a rudimentary cavity "imbedded" in the wall. We feel freer to make the suggestion because we ourselves made this error at first, and the possibility of error has been emphasized before.^{3, 13, 14} Of the descriptions of similar "trilocular" hearts, only those of Monserrat¹⁵ and Dudzus¹⁶ give convincing evidence that not more than one ventricular cavity was present. Hastings¹⁷ description leaves some doubt, but in a personal communication he assures us that in his case, also, a systematic search was made. Such cases may, of course, be functionally similar to those with a blind left ventricle.

*Pages 181-182.

The main series to be considered here extends somewhat beyond the narrower limits of the conditions represented by our own case, and includes cases of aortic and mitral stenosis, as well as other variants which may throw light on some aspects of the problem.

In the cases reviewed, the condition of the interventricular septum varies from certain absence¹⁵ and doubtful absence, through those with obvious defects and those with a mere cleft,¹⁸ to cases like ours, in which the septum was normal.¹⁹⁻²² In Donnally's²³ case, which was misapprehended by Abbott and Dawson,⁴ the septum was also complete. When the septum is adequately indicated, it varies considerably in position relative to the two ventricles, as well as to the great arteries. In the case of Schrader,²⁴ for instance, the anomaly was apparently of much later origin; the ventricles were more nearly of the same size, and the smaller left ventricle still reached to the apex. In all the other cases the large right ventricle formed the apex, and the septum was usually convex to the left. In Philpott's²⁰ case, however, the large right ventricle curved around the small left chamber, even more than in the normal heart. It is obvious that, if the left ventricle is much reduced, there will not be room for mitral and aortic valves of normal size and position. Some cases appear to be like ours in apparent displacement of the septum relative to the aortic or mitral ostia. These would almost surely include any in which a blind left ventricle may have been overlooked, but in which aortic or mitral valves are described in relation to the (right) ventricle.⁵ Usually, however, there is a general reduction of the left side of the heart, with a proportionate reduction of the (often atretic) valves, i.e., the interventricular septum clearly lies in its normal relation to the atrioventricular and arterial valves.^{23, 25, 26}

The morphologic complex of which our heart is the type calls for a defect of the interatrial septum if function is to continue. The only cases reviewed in which there was no such patency are those of McIntosh,⁸ in which there was compensation by abnormal communication of a pulmonary vein with the superior vena cava, and Bellet and Gouley,²⁷ in which the path of compensatory flow was doubtful and inadequate (patient died twelve hours after birth). Spolverini and Barbieri^{28*} had an almost complete closure of the foramen ovale. They assumed that the blood returned from the lungs through the bronchial veins! Lippincott's²⁵ assumption that there was no flow through a patent foramen ovale fails to take cognizance of the changes from the normal pattern of circulation entailed by this complex. In one case,²² with an aperture of only 0.2 cm., there was an associated aneurysmal bulge of the interatrial septum to the right, with thickening of the endocardium of the left side. Otherwise, there are consistent reports of considerable interatrial defects; but the size, form, and perhaps the morphologic significance of these defects are varied. In size they vary from small and perhaps inadequate openings^{29, 30† 2, 31‡} to large

*Case 7. †Case 4. ‡Case 1.

patencies, e.g., 14 mm.,³² or even absence of the septum.¹⁷ There is variation in shape of the foramen from a smooth, single hole, to a pair of holes²⁴ or even multiple openings.^{14, 15}

The term "foramen ovale" is loosely used for any interatrial opening, regardless of the developmental relations. Perhaps most of the cases reported are examples of true ostium secundum, but our own case suggests persistence of the ostium primum. In such cases the opening is close against the atrioventricular (cushion) septum anteriorly, so that there is no inferior or anterior limbus of the fossa, aside from the atrial floor and anterior wall. The rather wide fossa is about two-thirds closed by a crescentic membrane growing from the superior and posterior sides. The only description in this series which closely approximates ours is that of Sprenkel.¹⁸ If our diagnosis of ostium primum is correct, it would imply an early genesis of the defect.

The condition of the mitral valve varies from complete atresia^{11, 14, 18} through stenosis with thickened edges^{23, 30*} through a condition with tiny, but well-formed, cusps,^{19, 21} to an essentially normal valve. In the minute valve (either atretic or stenotic), chordae may be present^{9, 28†, 33} or absent.¹¹

The aorta in this series most often shows atresia of the ostium, together with hypoplasia from the root as far as the arch, with coronary vessels arising just above the atresia, and so receiving blood in reverse down the ascending aorta. There is variation, however, on all of these points. The atresia may be produced by a clear membrane²⁶ or by a membrane with the cusps still indicated,^{2, 10, 22} or there may be some distance between the blind root of the aorta and the ventricular cavity.¹⁹ In other cases^{30‡, 34, 35, 36§} there is incomplete fusion of the cusps, resulting in the persistence of a small passage. Again, in Donnally's²³ case, in spite of aortic and left-sided hypoplasia, there was only a narrowing of the mitral and aortic valves. The latter were well formed, so that the coronaries might have received enough blood by the normal route. In two cases,^{8, 11} only one coronary artery, the left, was found. In two others^{7, 37} the left coronary artery came from the pulmonary trunk. Gauss¹⁹ describes closure of the aorta for 2 cm., with a common coronary origin from the left ventricle. This was presumably not a case of ostial atresia. Ziegenspeck³⁸ also described obliteration of part of the ascending aorta by an organized thrombus, leaving a small chamber between this region and the atretic aortic ostium. He did not specify the origin of the coronaries which are figured. These variations of coronary origin, however, are few as compared with fifteen cases reviewed in which the condition was essentially like that in ours.

There are cases in this general series in which the ascending aorta was not extremely hypoplastic.^{16, 20, 28†} The two latter, however, were not cases of aortic atresia. Further, there are two cases of additional

*Case 4. †Case 7. ‡Case 2. §Group 3, Case 12.

coarctation of the aorta at a higher level, i.e., of the isthmus³⁷ and of the descending aorta.¹⁰

In general, the variations in the neck arteries which come from the aortic arch are matters of mere detail, and need not concern us here, although Philpott,²⁰ who says there are no anomalous vessels in this region, gives a sketch of vessels with most peculiar relationships.

The pulmonary trunk is almost always enlarged; it gives off normal branches to the lungs (also sometimes an anomalous coronary; previously mentioned), and continues into a widely patent ductus arteriosus. Of the five cases in which the ductus was closed or inadequate, all were among children whose ages exceeded the average life span for the group, and far beyond in three,^{16, 30*, 28†} i.e., thirteen months, two and one-half months, and forty days. In these three there was no aortic atresia, but Dudzus' citations of Jost³⁹ and Rokitansky⁴⁰ give no adequate explanation of the compatibility of an inadequate ductus with continued life.

The relation of the pulmonary to the aortic trunk varies as to the degree of "detorsion,"¹¹ but the exact orientation is hard to compare from one report to another, for, in these cases, it is difficult to find a common criterion for "ventral" or "left," because both the morphologically dorsal and ventral surfaces may be brought to the anatomic left by hypoplasia of the left atrium and ventricle. For instance, Wesson and Beaver,²¹ in both text and figure, represent the pulmonary arteries as coming from the ventral side of the pulmonary-ductus trunk, and this seems improbable in the morphologic sense. Further, their text does not mention the reverse twist of the pulmonary artery and aorta, as shown in their Fig. 2, where the course of the aorta lies anterior to the pulmonary artery. Have they artificially twisted these vessels through more than 180°? Again, Shapiro¹¹ shows a left pulmonary branch in surprising relation to the small aortic trunk.

The condition of the endocardium and valves on the left side varies considerably, but the cases tend to fall into two main groups: those like ours, with smooth, unthickened endocardium; and those with considerable alteration. Some descriptions omit mention of the endocardium, but, in this series, six cases are definitely in the former group. In the latter group, the commonest condition is a white, fibrous thickening of the left ventricular endocardium,^{22, 26, 27, 30‡, 32, 36§} usually involving the mitral valve remnant, and sometimes the left atrial endocardium and the aortic valve. Lippincott²⁵ speaks of hyaline fibrosis of the endocardium. Farber and Hubbard^{30*} and Mönckeberg³⁴ describe yellowish, elastic fibrosis. Myocardial changes have less often been mentioned, but in Farber and Hubbard's³⁰ first case there was scarring, as well as fatty alteration and calcification. Roberts³³ described left-sided myocardial atrophy and fibrosis, and Rukstinat¹⁰ described congestion

*Case 2. †Case 7. ‡Cases 1 and 4. §Group 3, Case 12.

and small hemorrhages in the left ventricular myocardium. It should be stressed that although some of these conditions may affect the ascending aorta as well, the right side of the heart is uniformly unaffected.

Abbott⁴¹ separates the cases of antenatal aortic stenosis (or atresia) which are caused by arrest of development from those of inflammatory origin, with the stenosis limited to the valves and the ventricular septum uninvolved. In the cases here reviewed, however, both normal endocardium and fibrosis were associated with either defective or normal ventricular septa. Thus, even if fibrosis of the endocardium or valves were to be considered as evidence of previous inflammation, the above classification could not hold for all cases. Further, Abbott's⁴² suggestion that the lesions are frequently syphilitic is apparently unfounded. In none of these cases were spirochetes demonstrated with metallic impregnation. Only in the case of Monserrat¹⁵ was there a history of maternal syphilis, and here no inflammatory process was detected in the heart. In the nine other cases^{11, 20, 26, 27, 30, 34, 36} in which an investigation was mentioned, regardless of the methods used, positive evidence for syphilis was lacking.

Although some of the above conditions may have been of inflammatory origin, especially those involving the myocardium, it is doubtful whether mere endocardial fibrosis or thickening of the valves is a true indication. Gross, in discussing Baggenstoss'²⁹ case, has emphasized the absence of critical histologic evidence, even when sought, in most cases in which fetal endocarditis was assumed. For a fuller discussion of the problem, we refer the reader to the papers of Loeser,²⁶ Bellet and Gouley,²⁷ and Farber and Hubbard.³⁰

The age at death in this group has a fairly smooth skew probability curve, with the mode at three days. The eight cases which scatter from eighteen days to twenty-one months, however, raise questions which cannot at present be answered. In two of these^{16, 28*} there were a patent aortic valve, an inadequate ductus, and a common ventricle. It is difficult to see how this structural pattern gives any functional advantage over that in the other cases, for in both the blood must have been completely mixed; unless, one might assume a special extension of Sabatier's theory of functional segregation of the streams of blood, which has been so well proved for the normal fetal circulation by the Barcroft school⁴³ and others. Three cases^{35, 44†} are too briefly described to indicate any reason for extended life, but there may have been some flow through the left ventricle. The same may be true of the case of Farber and Hubbard.^{30‡} Two other cases^{8, 15} in which death occurred at five weeks and three months, respectively, do not seem to be essentially different from the major series functionally, except for slight aortic patency in the former. The hypothesis of Roberts³³ that the length of life in these cases is proportional to the size of the interatrial

*Case 7. †Cases 2 and 3. ‡Case 2.

opening may be a fair generalization. The case of von Haam and Hartwell³² fits this, with an opening 14 mm. in diameter and a survival period of twelve days. An outstanding recent exception was Wiglesworth's²² case, with an opening only 2 mm. in diameter, but survival for eighteen days. It would seem, however, that with the characteristic pattern of complete stoppage of flow through the left ventricle, and complete mixing of blood in the right atrium, ventricle, and pulmonary trunk, even with adequate patency of the interatrial septum and the ductus, the expectation of life is not more than a week. Although dyspnea and cyanosis are characteristic, they are far from uniform from the time of birth.

In brief, this morphologic complex may be associated with indirect evidence of early inflammation, but more often is not. In the latter cases, at least, one should look for some early distortion of development. In our case we suspect that a misplacement of the interventricular septum, blocking the aortic ostium, was the primary defect. However, any influence which would check the flow through the mitral or aortic valves at an early enough stage might result in left-sided hypoplasia and atrophy and fusion of the valve cusps on the left. Mönckeberg¹³ formulated a hypothesis of asymmetric formation of the truncus septum, resulting in a small aorta with reduced flow. But in almost all of these cases, when the rudiments of aortic cusps are visible, there is an even, triradiate pattern like that in the enlarged pulmonary valve. Even a "bicuspid" aortic valve⁸ is caused by fusion of two of the three cusps. Evidently the septum has generally subdivided the ostium equally, and asymmetry developed later.

The variation in pattern is considerable; all cases show some deviation in detail from the general picture. Mönckeberg¹³ described the complex as *cor pseudotriloculare*, with rudimentary left ventricle and atresia of the aortic ostium and mitral valve. Two of his briefly described cases and two others^{14, 18} approach ours closely except for an interventricular defect. Otherwise, one of Mönckeberg's cases and ours seem to stand as close to the general condition as any yet described; we would call this condition complete closure of the left ventricle by aortic and mitral atresia, with left-sided and aortic hypoplasia, compensating interatrial and ductus patencies, and without evidence of early inflammation.

SUMMARY

A case of congenital mitral and aortic atresia, associated with hypoplasia of the left atrium and ventricle and compensating patencies of the interatrial foramen and ductus arteriosus, is described. The anomaly is attributed to a developmental misplacement of the interventricular septum. No evidence was found to indicate an inflammatory cause for the defect.

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THE EFFECT OF OXYGEN ON THE ELECTROCARDIOGRAMS OF CYANOTIC PATIENTS

JOHN N. EDSON, M.D.
BROOKLYN, N. Y.

EXPERIMENTALLY induced anoxemia is known to produce alterations in the RS-T segments and T waves of the electrocardiograms of patients with coronary insufficiency.¹⁻⁵ It was believed that the administration of oxygen to patients with myocardial anoxia, caused either by coronary insufficiency or generalized anoxemia, might produce converse alterations of these deflections. Although superficial anoxia, as manifested by cyanosis, is not necessarily an index of myocardial anoxia, it seems reasonable to assume that, when cardiac insufficiency or a recent coronary occlusion is the underlying cyanosis-producing factor, at least some degree of cardiac anoxia is present. Consequently, an investigation has been made of the effects of oxygen inhalation on the electrocardiograms of cyanotic patients.

Forty-two cyanotic patients whose anoxia-producing factor was cardiac insufficiency, recent coronary occlusion, a pulmonary lesion, or a combination of these, and twenty noncyanotic controls, ten with heart disease and ten without, were chosen for this study. With the development of cyanosis (usually on admission to the hospital), oxygen was administered by the nasal route at the rate of ten liters per minute for one-half hour. Electrocardiograms were recorded before, and at the end of, the period of inhalation. The oxygen was then discontinued when the patient's condition permitted (eight patients were considered too critically ill to justify its discontinuation). Thirty minutes later a third control electrocardiogram was taken; this served to prevent mistaking progressive alterations, especially those associated with recent coronary occlusion, for alterations produced by oxygen therapy. The position of the precordial electrode was carefully marked, so that it could be exactly replaced for recording successive tracings. The limb electrodes were left in place. In this manner, alterations produced by varying the location of the electrode were eliminated.

After having compensated for the slight differences in standardization, these tracings were compared, and only those alterations in the second electrocardiogram which disappeared in the third and measured 0.5 millimeter or more in amplitude were considered significant.

OBSERVATIONS

Among the forty-two cyanotic patients there were thirty-three men and nine women. Their ages ranged from thirty-two years to seventy-four years, and averaged fifty-six years. They were classified in four groups, according to the factor which produced the cyanosis: (1) those with recent coronary occlusion, (2) those with cardiac insufficiency with-

From the Department of Internal Medicine, Long Island College of Medicine, and the Medical Service of the Long Island College Hospital, Brooklyn, New York.

Received for publication April 27, 1942.

out recent coronary occlusion, (3) those with a pulmonary cyanosis-producing lesion, and (4) those with both cardiac insufficiency and a pulmonary lesion. Their electrocardiograms varied considerably in configuration. Six patients had normal tracings; twenty had electrocardiograms with evidence of varying degrees of myocardial disease, indefinite in character; eight had the electrocardiographic pattern of recent myocardial infarction; and six had bundle branch block.

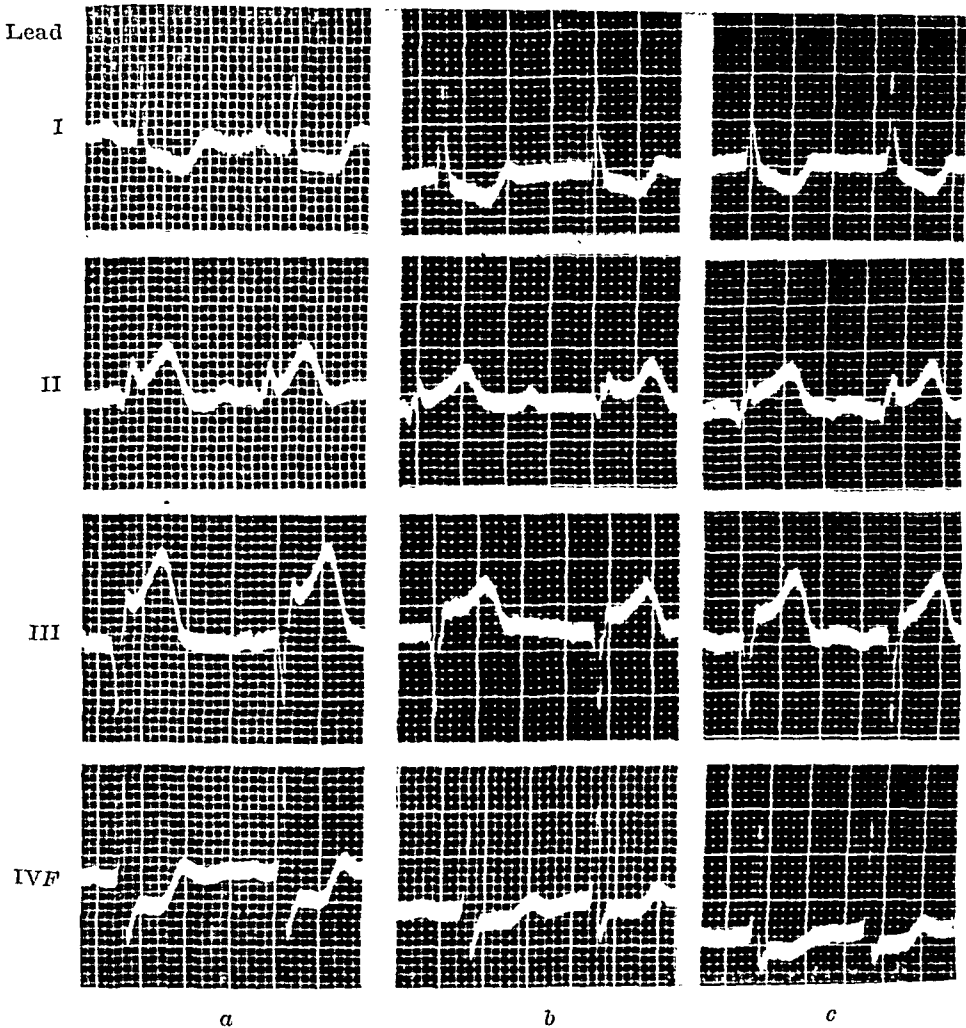


Fig. 1.—Case 42. Electrocardiograms showing the configuration indicative of posterior wall infarction, recorded (a) before oxygen administration, (b) after one-half hour of oxygen inhalation, and (c) one-half hour after oxygen therapy had been discontinued. Significant alterations are found in Leads II, III, and IVF.

The observations which were made on the electrocardiograms of these forty-two patients follow:

1. Alterations were noted in the tracings of twenty-nine patients.
2. These changes were limited to elevation or depression of the RS-T segments and the T waves.
3. The greatest alterations appeared in the T waves, particularly those of Lead IVF.
4. The greatest RS-T segment deviation measured 1.5 millimeters, whereas the greatest T-wave change measured 4.0 millimeters.

5. These alterations varied in direction and extent and did not necessarily, as one might expect, show a reversion toward normal, even in those electrocardiograms with a configuration diagnostic of myocardial infarction.

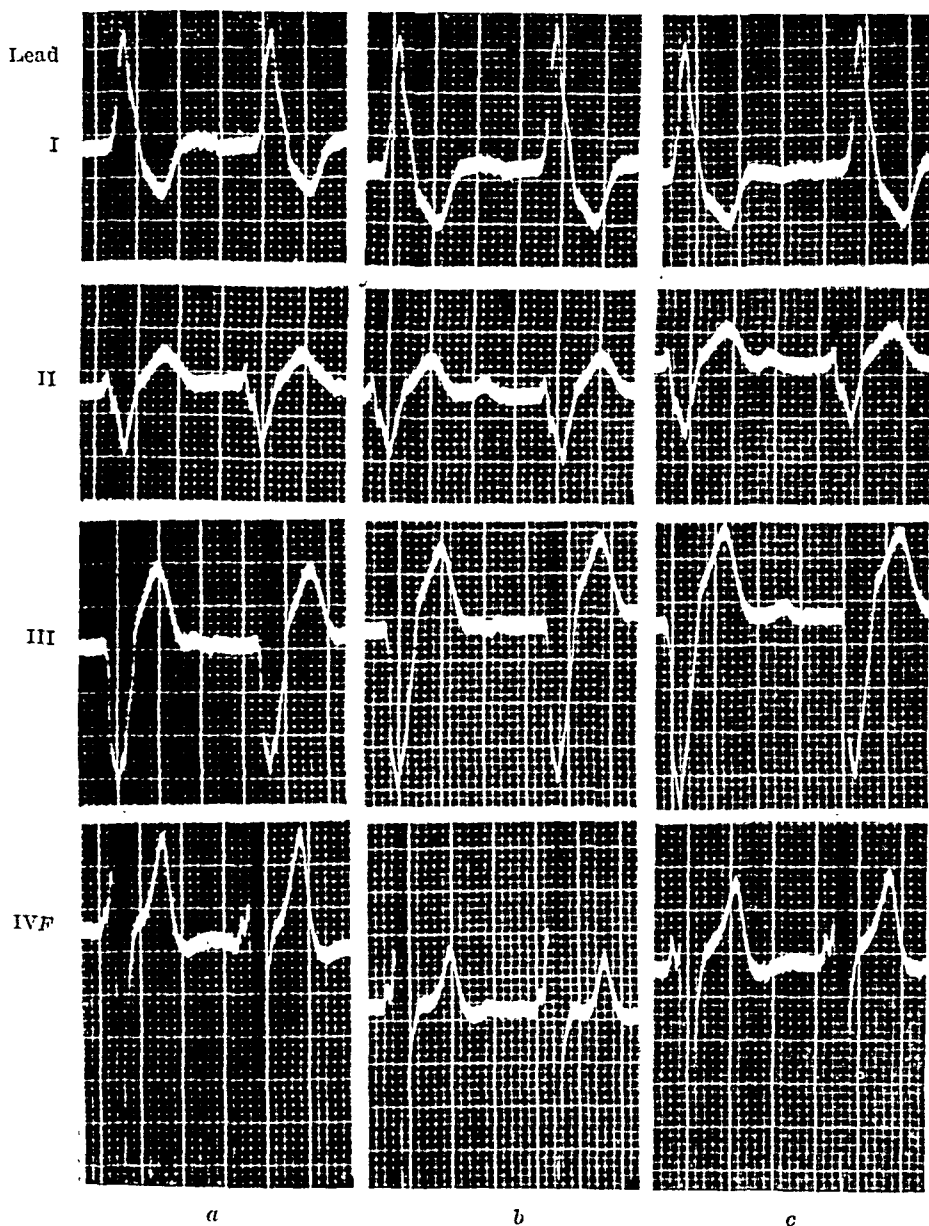


Fig. 2.—Case 36. Electrocardiograms with the configuration of left bundle branch block, recorded (a) before oxygen administration, (b) after one-half hour of oxygen inhalation, and (c) one-half hour after oxygen therapy had been discontinued. Significant alterations are found in Lead IVF.

6. RS-T segment alterations were found in the tracings of thirteen patients, and five of these had changes in more than one lead. Three-fourths of the alterations were directed toward the isoelectric line, and one-fourth away from it.

TABLE I

THE EFFECT OF OXYGEN ON THE ELECTROCARDIOGRAMS OF
CYANOTIC PATIENTS

NO.	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	DEGREE OF CYANOSIS	RELIEF OF CYANOSIS	RHYTHM	SIGNIF- ICANT ALTERA- TIONS
1	69	Coronary occlusion Diabetes mellitus	Myocardial infarction	Slight	Improved	RSR	+
2	57	Coronary occlusion Hypertensive card.— vas. dis.	Myocardial infarction	Slight	Relieved	RSR	+
3	47	Coronary occlusion Hypertensive card.— vas. dis. Cardiac insufficiency	Myocardial infarction	Moderate	Improved	RSR	+
4	60	Coronary occlusion Diabetes mellitus	Myocardial infarction	Slight	Relieved	RSR	+
5	48	Rheumatic heart dis- ease Cardiac insufficiency	Vent. myo- card. dis.	Slight	Relieved	RSR	0
6	57	Rheumatic heart dis- ease Cardiac insufficiency Pulmonary infarction	Vent. myo- card. dis.	Marked	Improved	AF	+
7	32	Lobar Pneumonia Acute pericarditis	Vent. myo- card. dis.	Moderate	Improved	RSR	+
8	60	Coronary occlusion	Myocardial infarction	Slight	Relieved	RSR	+
9	61	Bronchopneumonia Diabetes mellitus	Vent. myo- card. dis.*	Marked	Relieved	RSR	0
10	60	Hypertensive card.— vas. dis. Cardiac insufficiency Diabetes mellitus	Left bundle branch block	Marked	Improved	RSR	+
11	62	Coronary occlusion Hypertensive card.— vas. dis.	No abnor- malities	Moderate	Improved	RSR	+
12	57	Rheumatic heart dis- ease Cardiac insufficiency	Vent. myo- card. dis.	Marked	Improved	RSR	+
13	54	Coronary occlusion	Myocardial infarction	Slight	Relieved	RSR	+
14	73	Bronchopneumonia	Vent. myo- card. dis.*	Marked	Relieved	RSR	0
15	45	Atelectasis Carcinoma of lung	Vent. myo- card. dis.*	Marked	Improved	RSR	+
16	49	Hypertensive card.— vas. dis. Cardiac insufficiency Bronchopneumonia Bronchial asthma	Vent. myo- card. dis.	Marked	Improved	RSR	+
17	57	Lobar pneumonia Empyema Hypertensive card.— vas. dis.	Left bundle branch block	Marked	Relieved	RSR	+

*A clinical diagnosis of heart disease has not been made in these cases, despite the finding of electrocardiographic abnormalities, because these abnormalities were slight, they were present in older individuals, in whom myocardial fibrosis is common, and they were not associated with any other clinical evidence of heart disease.

TABLE 1—CONT'D

NO.	AGE	CLINICAL DIAGNOSIS	ECG DIAGNOSIS	DEGREE OF CYANOSIS	RELIEF OF CYANOSIS	RHYTHM	SIGNIFICANT ALTERATIONS
18	51	Lobar pneumonia Tertiary syphilis	No abnormalities	Marked	Improved	RSR	+
19	51	Coronary occlusion Syphilitic heart disease Cardiac insufficiency	Vent. myocard. dis. Digitalis	Marked	Relieved	RSR	+
20	74	Asthmatic bronchitis	Vent. myocard. dis.*	Marked	Relieved	RSR	+
21	65	Hypertensive card.— vas. dis. Cardiac insufficiency Diabetes mellitus	Vent. myocard. dis.	Moderate	Relieved	AF	+
22	65	Hypertensive card.— vas. dis. Cardiac insufficiency	Vent. myocard. dis.	Moderate	Improved	AF	0
23	36	Coronary occlusion	Myocardial infarction	Slight	Improved	RSR	+
24	59	Lobar pneumonia	No abnormalities	Marked	Improved	RSR	0
25	35	Hypertensive card.— vas. dis. Cardiac insufficiency Gremia	No abnormalities	Marked	Improved	RSR	0
26	53	Bronchopneumonia	Vent. myocard. dis.*	Marked	Improved	RSR	+
27	65	Coronary occlusion	Right bundle branch block	Marked	Improved	Idiovent.	+
28	51	Coronary occlusion	Vent. tachycardia	Moderate	Relieved	Vent. Tach.	+
29	51	Arteriosclerotic heart dis. Syphilis Lobar pneumonia	No abnormalities	Marked	Relieved	RSR	0
30	53	Arteriosclerotic heart dis. Cardiac insufficiency	Aur. tachycardia	Marked	Relieved	Aur. Tach.	0
31	62	Rheumatic heart disease Cardiac insufficiency	Vent. myocard. dis.	Moderate	Relieved	AF	0
32	65	Arteriosclerotic heart dis. Cardiac insufficiency	Vent. myocard. dis.	Moderate	Relieved	AF	0
33	61	Coronary occlusion	Right bundle branch block	Marked	Improved	RSR	+
34	57	Arteriosclerotic heart dis. Hypertensive card.— vas. dis. Cardiac insufficiency	Vent. myocard. dis.	Moderate	Relieved	RSR	0
35	66	Lobar pneumonia	Vent. myocard. dis.*	Moderate	Relieved	RSR	0

TABLE I—CONT'D

NO.	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	DEGREE OF CYANOSIS	RELIEF OF CYANOSIS	RHYTHM	SIGNIFICANT ALTERATIONS
36	74	Arteriosclerotic heart dis. Hypertensive card.—vas. dis. Cardiac insufficiency	Left bundle branch block	Moderate	Improved	RSR	+
37	55	Arteriosclerotic heart dis. Hypertensive card.—vas. dis. Cardiac insufficiency	Vent. myo-card. dis.	Moderate	Improved	Aur. Flut.	+
38	54	Thrombosis of heart Bronchopneumonia	Vent. myo-card. dis.	Marked	Relieved	RSR	+
39	69	Bronchial asthma Emphysema Cor. pulmonale Cardiac insufficiency	No abnormalities	Marked	Improved	RSR	+
40	69	Syphilitic heart disease Bronchopneumonia Cardiac insufficiency	Left bundle branch block	Moderate	Relieved	RSR	+
41	54	Coronary occlusion	Vent. myo-card. dis.	Marked	Relieved	RSR	+
42	56	Coronary occlusion	Myocardial infarction	Slight	Relieved	RSR	+

7. T-wave alterations were noted in the tracings of twenty-six patients, and ten of these had changes in more than one lead. One-half of these alterations represented an increase in positivity or a decrease in negativity, whereas the other half showed a decrease in positivity or an increase in negativity.

8. Alterations were found in the tracings of all of the fourteen patients with recent coronary occlusion.* Fourteen RS-T segment alterations were found in seven cases (five had alterations in more than one lead); the greatest change in amplitude was 1.5 millimeters, and the average was 0.7 millimeter. Twenty-one T-wave changes were present in twelve cases (five had changes in more than one lead); the greatest alteration in amplitude measured 3.0 millimeters, and the average was 1.1 millimeters.

9. Alterations were found in the tracings of five of the twelve patients with cardiac insufficiency without recent coronary occlusion. RS-T segment alterations in one lead were found in two cases; one measured 1.5 millimeters in amplitude, and the other, 0.5 millimeter. T-wave alterations in one lead were present in four cases; the greatest measured 4.0 millimeters in amplitude, and the average was 1.5 millimeters.

10. Alterations were found in the tracings of three of the eight patients whose cyanosis-producing factor was a pulmonary lesion. Only

*The admission electrocardiograms (used in this study) of six of these patients were not diagnostic of myocardial infarction, but serial tracings, together with other clinical and laboratory data, proved to be convincing evidence of recent coronary occlusion.

one RS-T segment change was present in this group; it measured 0.5 millimeter in amplitude. Six T-wave alterations were present in three cases (two patients had changes in more than one lead); the greatest measured 1.0 millimeter in amplitude, and the average was 0.6 millimeter.

11. Alterations were found in the tracings of seven of the eight patients whose cyanosis was produced by a combination of cardiac insufficiency and a pulmonary lesion. RS-T segment alterations in one lead were found in two cases; one measured 1.0 millimeter in amplitude, and the other, 0.5 millimeter. Twelve T-wave alterations were present in seven cases (three patients had changes in more than one lead); the greatest measured 2.7 millimeters in amplitude, and the average was 0.9 millimeter.

12. There was no correlation either between the degree of cyanosis and the number or degree of the electrocardiographic changes, or between the extent of the clearing of cyanosis produced by oxygen and these alterations.

13. There were alterations in all of the six cases in which the electrocardiograms conformed to the pattern of bundle branch block.

14. No alterations were observed in any RS-T segment whose take-off was isoelectric.

15. The presence or absence of electrocardiographic modifications bore no apparent relation to prognosis.

The noncyanotic controls, composed of sixteen men and four women, ranged in age from twenty-nine years to sixty-eight years; the average was 44.7 years. They were divided into two groups, those with clinical and laboratory evidence of compensated heart disease, and those without any evidence of cardiac abnormalities. The electrocardiograms of the compensated cardiacs showed evidence of myocardial damage in all but one case, whereas the tracings of the patients without heart disease were all normal.

The electrocardiograms taken on the noncyanotic controls revealed:

1. No alterations in the tracings of the ten compensated cardiac patients.

2. An elevation of the T wave in three of the ten patients with no evidence of heart disease, and an elevation of the RS-T segment in one of these three.

3. No relation between the age of the patient and the changes produced in either the cyanotic or the noncyanotic group.

DISCUSSION

From these observations it becomes apparent that inhalation of oxygen altered the cardiac physiology of 69 per cent of these cyanotic patients in such a manner and to such an extent as to be demonstrable in serial electrocardiograms. Among the noncyanotic controls, however,

TABLE II

AN ANALYSIS OF THE RS-T SEGMENTS, THE T WAVES, AND THEIR CORRESPONDING ALTERATIONS IN THE ELECTROCARDIOGRAMS OF THE CYANOTIC PATIENTS WHOSE TRACINGS SHOWED SIGNIFICANT DEFLECTIONS

CASE NO.	RS-T SEGMENTS												T WAVES			
	AMPLITUDE OF ORIGINAL DEFLECTION*				ALTERATION PRODUCED BY OXYGEN*				AMPLITUDE OF ORIGINAL DEFLECTION*				ALTERATION PRODUCED BY OXYGEN*			
	LEAD				LEAD				LEAD				LEAD			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
1	0	-1.0	-1.0	+1.0	0	0	+0.5	-0.5	-1.5	+1.0	+2.5	-1.0	0	0	0	0
2	-0.5	+1.5	+1.5	-2.0	0	-0.5	-0.5	+1.0	+1.1	+3.5	+4.0	-5.0	+0.8	-1.4	-3.0	+3.0
3	0	0	0	+7.5	0	0	0	0	-0.5	-1.0	-0.5	-2.0	0	+0.5	0	+1.5
4	+1.5	0	-1.0	+8.0	0	0	0	+1.5	+1.5	+1.0	+1.0	+9.2	0	0	0	+1.7
6	+0.7	-0.7	-1.0	+2.0	0	0	0	-1.0	+0.9	-0.5	-1.5	+4.0	0	0	0	-1.0
7	+1.5	+1.0	-0.2	+1.0	+0.5	0	0	0	+5.0	+4.5	-0.5	+7.0	0	+0.5	0	0
8	-1.0	+1.0	+1.5	-2.2	0	0	0	0	+1.8	-1.5	-3.2	+7.5	0	0	-0.5	0
10	0	+0.5	+1.0	+4.0	0	0	0	-0.5	+1.0	+3.0	+2.5	+12.0	0	0	0	0
11	0	0	+0.5	0	0	0	0	0	+1.5	+1.5	0	+3.5	0	0	0	+0.5
12	0	-0.3	-0.5	+0.5	0	0	0	0	+1.0	-1.2	-1.5	+2.0	+0.5	0	0	0
13	+1.5	+0.8	-0.5	+4.5	0	0	0	+0.5	+1.8	+2.0	+1.5	+7.0	0	0	0	0
15	0	0	0	+0.5	0	0	0	0	+1.0	+2.0	+1.5	+1.5	-0.5	-0.6	0	0
16	0	0	0	-1.0	0	0	0	0	+1.5	+2.0	+1.5	+0.5	-0.5	-0.8	-1.0	+0.5
17	+1.0	0	0	+2.0	0	0	0	+0.5	+3.8	+1.8	-2.0	+9.0	0	0	+1.0	-2.7
19	-1.0	-1.0	-0.5	+0.5	0	0	0	-0.5	+0.5	-2.5	0	+3.0	-0.5	0	+1.0	-1.0
20	0	-2.0	0	-2.0	0	0	0	0	+0.5	+1.0	+1.5	+3.0	0	0	0	0
21	0	0	0	0	0	0	0	0	+0.5	+2.0	0	+0.5	0	0	0	-1.0
23	0	+0.3	+0.7	-1.0	0	0	0	0	+2.0	+2.0	0	+4.0	0	0	0	+1.0
26	0	0	0	0	0	0	0	0	+1.5	+1.5	0	0	+0.5	+0.5	0	0
27	0	-0.5	-0.7	+5.9	-0.5	0	-0.8	+0.5	+1.2	-2.5	-3.0	+8.5	0	0	0	+0.5
28	+4.0	-1.0	0	+2.5	0	0	0	-1.0	+4.5	+1.2	-2.8	+4.5	-0.5	0	+1.5	0
33	-0.5	+0.5	+0.6	+1.0	0	0	0	0	+1.2	-2.2	-3.0	-1.0	+0.5	+1.2	0	0
36	-3.0	+0.5	+3.5	+1.5	0	0	0	-1.5	+5.5	+3.5	+8.5	+12.5	0	0	0	-4.0
37	+0.3	+0.2	-0.3	+0.5	0	0	0	0	-5.5	+1.0	+1.0	+1.0	0	0	0	+0.5
38	0	+0.5	-0.8	+1.0	0	0	0	0	+1.0	+1.5	+1.2	+1.6	0	0	0	0
39	+0.5	+0.5	+0.3	+0.5	0	0	0	0	+0.9	+1.5	+1.2	+4.1	0	0	0	+0.6
40	0	0	0	0	0	0	0	0	+1.6	+2.0	-0.5	+1.2	0	0	0	+0.7
41	-0.5	-1.5	0	+2.0	0	0	0	0	+1.8	+2.0	+1.2	-1.9	0	-0.8	-0.8	0
42	-1.3	+1.5	+4.0	-3.7	0	0	-0.5	+0.6	-2.7	+5.5	+9.2	-8.2	0	-0.8	-1.8	+1.5

*Measured in millimeters.

TABLE III

AN ANALYSIS OF THE RS-T SEGMENTS, THE T WAVES, AND THEIR CORRESPONDING ALTERATIONS IN THE ELECTROCARDIOGRAMS OF THE NORMAL, NONCYANOTIC SUBJECTS WHOSE TRACINGS SHOWED SIGNIFICANT DEFLECTIONS

CASE NO.	RS-T SEGMENTS										T WAVES									
	AMPLITUDE OF ORIGINAL DEFLECTION*					ALTERATION PRODUCED BY OXYGEN*					AMPLITUDE OF ORIGINAL DEFLECTION*					ALTERATION PRODUCED BY OXYGEN*				
	LEAD					LEAD					LEAD					LEAD				
	I	II	III	IV		I	II	III	IV		I	II	III	IV		I	II	III	IV	
1	+0.5	+1.0	+0.5	0		0	0	0	0		+2.0	+3.2	+1.2	+1.2		0	0	0	0	
4	+0.2	+0.3	+0.2	+0.5		0	0	0	+0.5		+1.2	+0.7	-0.3	+3.0		0	+0.7	0	+0.8	
10	+0.2	0	0	+0.3		0	0	0	0		+0.5	+0.8	+0.2	+2.0		0	0	0	+0.5	

*Measured in millimeters.

such modifications were present in only 15 per cent of the cases. That these alterations were not proportional to the degree of cyanosis or to the extent of its improvement with oxygen therapy is understandable, for it is known that there is no constant relationship between peripheral and coronary anoxemia.

It is notable that frequent varying alterations, in either a positive or a negative direction, were found in abnormal electrocardiograms, whereas only a few changes, all in the direction of increased positivity, were found in normal tracings. This observation suggests that the production, by oxygen, of physiologic changes in the myocardium sufficient to alter the electrocardiogram depends largely upon the presence and the extent of myocardial damage. The fact that electrocardiographic modifications were observed in every case of recent coronary occlusion and in every case of bundle branch block offers further support to such an hypothesis.

It was observed that the alterations produced by inhaling oxygen frequently did not show the expected reversion toward normal, particularly in the cases of recent coronary occlusion. Thus, depression of an RS-T segment or an increase in the negativity of a T wave, ordinarily indicative of myocardial disease or toxicity, may also be produced by the therapeutic agent, oxygen. The explanation for this unexpected, as well as the expected, response to the inhalation of oxygen may possibly be found in the varying degree of oxygenation of normal as compared with damaged myocardium. On the one hand, an increase in oxygenation may be greater in normal areas than in abnormal areas of the myocardium. Such a combination of circumstances would accentuate the abnormalities of the electrocardiogram, for it would increase already existing differences. An inverted T wave, for example, would be further depressed. On the other hand, the increase in oxygenation may be greater in damaged areas than in normal areas of the myocardium. In this case the electrocardiographic abnormalities would be decreased, and thus an inverted T wave would tend to right itself. The main factor governing the degree of oxygenation of normal as compared to damaged myocardium is the patency of the coronary arteries.

This study, therefore, offers further evidence in proof of the hypothesis that changes in the degree of oxygenation of the myocardium tend to produce alterations in the electrocardiogram, and that these alterations are confined to the RS-T segments and the T waves in all four leads; and it further points out that the effect of oxygen on the anoxia of a diseased heart is not expressed in the electrocardiogram by any set pattern, but rather by a variety of patterns which probably depend largely upon the state of health and oxygenation of the individual muscle bundles of the myocardium.

SUMMARY

1. Observations were made on the effect of oxygen therapy on the electrocardiograms of forty-two patients whose cyanosis-producing factor was cardiac insufficiency, recent coronary occlusion, a pulmonary lesion, or a combination of these, and twenty noncyanotic controls, ten with compensated heart disease and ten without heart disease.

2. Alterations were noted in the electrocardiograms of twenty-nine (69 per cent) cyanotic patients and in only three (15 per cent) of those of noncyanotic controls.

3. The alterations were confined to the RS-T segments and the T waves.

4. In abnormal tracings the changes were expressed by either an increase or a decrease in positivity or negativity of the deflections, whereas in normal tracings they were manifested only by an increase in positivity.

5. Alterations were noted in all fourteen cases of recent coronary occlusion and in all six cases of bundle branch block.

6. This study offers support to the hypothesis that changes in the degree of oxygenation of the myocardium tend to produce alterations in the electrocardiogram.

7. It further points out that the lack of uniformity of alterations in abnormal electrocardiograms is probably due to the varying state of health and oxygenation of the individual muscle bundles of the myocardium.

The author wishes to express his appreciation to Dr. Tasker Howard, Professor of Medicine, for his guidance and helpful criticism, and to Mrs. Frances Edson for her technical assistance.

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THE USE OF HEPARIN FOR THE COMPLICATIONS WHICH FOLLOW SCLEROSING OF VARICOSE VEINS BY MASSIVE INJECTION

SAMUEL H. SEDWITZ, M.D.
YOUNGSTOWN, OHIO

IN 1938, a surgical procedure for sclerosing varicose veins by the massive injection of one dose of sodium ricinoleate was presented.¹ This procedure proved to be extremely efficient. We have found that the process is attended by one undesirable side reaction, namely, postoperative edema which lasts for a period of three to five weeks in 10 to 12 per cent of cases. This occurred in spite of every precaution to ascertain the preoperative condition of the deep venous circulation.*

In our earlier experiences, we attempted to combat this undesirable postoperative complication by mecholyl iontophoresis, plus prostigmin by subcutaneous injection, whirlpool baths, the oscillating bed with intermittent venous compression, and bandaging. Amelioration of symptoms was always obtained, but the treatment took too long. In spite of early institution of treatment, the symptoms grew in severity for two or three days before there was evidence of improvement.

In attempting to evaluate the mechanism responsible for this edema after the massive injection of sclerosing material, we found that the thrombosis which occurred at the site of the induced chemical phlebitis had a tendency to extend beyond the field in which thrombosis was desired, i.e., to the communicating veins and even the deep veins, in spite of the fact that only superficial veins were injected. Although chemical thrombosis and phlebitis are desirable in order to obliterate the varicose veins, prevention of the extending thrombosis would greatly enhance the value of the operation.

It occurred to us, therefore, that a simple method of controlling the extent of thrombosis would be to use heparin. From experimental and clinical observations we know that simple thrombosis occurs within twelve hours. Recently, an opportunity was afforded to examine veins which had been sclerosed by this method sixteen hours after injection (the patient was accidentally killed). We found that the long saphenous vein was sclerosed almost to the ankle with a firm clot. But, in addition, the communicating branches above and below the knee also showed some phlebitis (chemical), and a small amount of clot was adherent

Peripheral Vascular Clinic, Youngstown Hospital Association.
Received for publication April 30, 1942.

*Since this paper was written, another preoperative test has been used to ascertain the status of the deep venous circulation. A venogram is made by injecting 20 c.c. of diodrast (35 per cent solution) in the lesser saphenous vein at the ankle. This is done in every case of edema resulting from varicose veins (other causes ruled out), and when there is the slightest question of a previous thrombophlebitis. This procedure in detail will be published soon.

to the intima but was not completely sclerosing the vessel. The thrombosis obviously was extending. The next day our examination probably would have suggested the advisability of using heparin. In view of the fact that the clotting which follows chemical phlebitis in the treatment of varicose veins is desirable, heparinization was not instituted until twenty-four hours after injection of the sclerosing material. It is important to remember that heparin does not dissolve a thrombus but prevents further clotting and extension of the thrombosis.

PROCEDURE

Immediately after operation and injection, the legs are wrapped in elastic bandages from the toes to the knee, and the patient walks from the operating room, either to his room in the hospital or to the car or bus taking him home. During the next ten to twelve hours he is instructed to walk for ten minutes every hour until retiring. During this period, treatment of pain consists of local cold compresses with or without witch hazel and analgesics.

The following day the patient reports for examination, and certain facts regarding the status of the venous circulation are ascertained. Measurements of the legs are compared with preoperative measurements. Heparin therapy, plus the usual regimen, is instituted if the following indications are present: (1) marked swelling of the entire injected leg, with an increase in circumference of one-half inch at the ankle, one inch at the calf, and two inches at mid thigh; (2) tenderness and discoloration of the skin over and about the veins; (3) sharp, cramp-like pains along veins radiating to the inguinal and lower abdominal regions; (4) impaired circulatory function in the leg, as shown by tests (Oschner-Mahorer-oscillometric, circulation time, venous pressure, increase in sedimentation time, and leucocytosis).

Heparin is given in doses of 10,000 units intravenously every four hours. It is not given by continuous infusion because the patient is confined in an oscillating bed. The clotting time is taken before each injection, and when it reaches ten to twelve minutes the heparin treatment is discontinued, but the usual treatment which is required for two or three days after cessation of pain to relieve the edema is not discontinued.

RESULTS

Fourteen patients were treated with heparin, in addition to the usual treatment. Pain was relieved in most cases four hours after the first injection of heparin, and never later than after the second injection (eight hours). Likewise, there was no evidence of increasing circulatory embarrassment after the second injection. The undesirable postoperative sequelae in all cases disappeared at the most in five days, and the patients left the hospital. This is a vast improvement over the results in twenty-nine cases with the usual routine before heparin was added

to the treatment. Without heparin, the symptoms increased in severity, regardless of treatment, for two or three days. Hospitalization for two to three weeks was necessary, and the treatment was continued thereafter for two or three weeks at the clinic before complete recovery was accomplished.

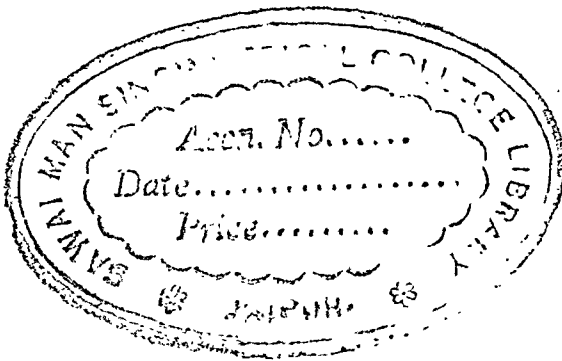
CONCLUSION

We feel that the addition of heparin to our usual regimen of treatment of the complications which follow sclerosing of varicose veins by massive injection has improved the value of the procedure because it reduces the postoperative disability, pain, and extensive destruction of the venous circulation.

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Heparin, in the form of liquamin, and prostigmin methylsulfate were generously supplied by Roche-Organon and Hoffmann-La Roche, respectively, Nutley, New Jersey.



THE ELECTROCARDIOGRAM AFTER STANDARD EXERCISE AS A FUNCTIONAL TEST OF THE HEART

ARTHUR M. MASTER,* M.D., RUDOLPH FRIEDMAN, M.D., AND
SIMON DACK,† M.D.
NEW YORK, N. Y.

AN OBJECTIVE test of cardiac function is of importance in distinguishing functional from organic heart disease. It is useful in diagnosis and is helpful in studying the progress of disease and the degree of physical disability. It is of particular value when other examinations of the heart are negative, i.e., physical examination, electrocardiogram, fluoroscopy, exercise tolerance test, etc.

The test to be described in this report consists of recording an electrocardiogram after a definite amount of work, standardized for the patient's age, sex, and weight.¹⁻⁴ It is essential to utilize a standard amount of work; for even healthy persons, if they exercise to excess, may have abnormal electrocardiographic responses.⁵⁻¹⁰ It is therefore important that the exertion to which the patient is subjected will not produce abnormal electrocardiographic changes in any healthy person. This has been verified for the standard two-step test. In addition to recording the electrocardiogram after the two-step test, the patient's exercise tolerance can be measured in the ordinary way, that is, by obtaining blood pressure and pulse rate readings before and after exercise.^{1, 2}

PROCEDURE AND MATERIAL

The number of climbs on the steps which the patient performs is obtained from previously prepared tables² based on sex, age, and weight (Tables I and II). Two steps, each nine inches high, totaling eighteen inches, are climbed a prescribed number of times by the patient in exactly one and one-half minutes. An electrocardiogram is taken immediately on cessation of the exercise and repeated three minutes and then eight minutes later, and these tracings are compared with the control tracing, made before commencing the trips on the steps. In actual performance, the electrodes are strapped on the patient's arm, left leg, and precordium (Fig. 1).

We often have the patient make double the number of trips when the standard exercise gives a negative test. That is, an hour later, or the next day, the test is repeated with twice the number of ascents in exactly three minutes. In other words, the same rate of work is continued, but twice the amount is performed. We have ascertained that the doubled two-step exercise does not result in significant electrocardiographic changes in healthy persons. Work beyond this, either by quickening the rate of climb or prolonging the period, may produce electrocardiographic alterations in normal people.⁵⁻¹⁰

An abnormal response in the electrocardiogram is considered to be depression of the RS-T segment of more than 0.5 mm. below the isoelectric line or an alteration

From the Cardiographic Laboratory, The Mount Sinai Hospital, New York.

Received for publication May 10, 1942.

*Comdr., M. C., U. S. N. R.

†Capt., M. C., U. S. A.

TABLE I
STANDARD NUMBER OF ASCENTS FOR MALES*

WEIGHT (LB.)	AGE IN YEARS												
	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
40-49	35	36											
50-59	33	35	32										
60-69	31	33	31										
70-79	28	32	30										
80-89	26	30	29	29	29	28	27	27	26	25	25	24	23
90-99	24	29	28	28	28	27	27	26	25	25	24	23	22
100-109	22	27	27	28	28	27	26	25	25	24	23	22	22
110-119	20	26	26	27	27	26	25	25	24	23	23	22	21
120-129	18	24	25	26	27	26	25	24	23	23	22	21	20
130-139	16	23	24	25	26	25	24	23	23	22	21	20	20
140-149		21	23	24	25	24	24	23	22	21	20	20	19
150-159		20	22	24	25	24	23	22	21	20	20	19	18
160-169		18	21	23	24	23	22	22	21	20	19	18	18
170-179			20	22	23	23	22	21	20	19	18	18	17
180-189			19	21	23	22	21	20	19	19	18	17	16
190-199			18	20	22	21	21	20	19	18	17	16	15
200-209				19	21	21	20	19	18	17	16	16	15
210-219				18	21	20	19	18	17	17	16	15	14
220-229				17	20	20	19	18	17	16	15	14	13

TABLE II
STANDARD NUMBER OF ASCENTS FOR FEMALES*

WEIGHT (LB.)	AGE IN YEARS												
	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
40-49	35	35	33										
50-59	33	33	32										
60-69	31	32	30										
70-79	28	30	29										
80-89	26	28	28	28	28	27	26	24	23	22	21	21	20
90-99	24	27	26	27	26	25	24	23	22	21	20	19	18
100-109	22	25	25	26	26	25	24	23	22	21	20	19	18
110-119	20	23	23	25	25	24	23	22	21	20	19	18	18
120-129	18	22	22	24	24	23	22	21	20	19	19	18	17
130-139	16	20	20	23	23	22	21	20	19	19	18	17	16
140-149		18	19	22	22	21	20	19	19	18	17	16	16
150-159		17	17	21	20	20	19	19	18	17	16	16	15
160-169		15	16	20	19	19	18	18	17	16	16	15	14
170-179		13	14	19	18	18	17	17	16	16	15	14	13
180-189			13	18	17	17	17	16	16	15	14	14	13
190-199			12	17	16	16	16	15	15	14	13	13	12
200-209				16	15	15	15	14	14	13	13	12	11
210-219				15	14	14	14	13	13	13	12	11	11
220-229				14	13	13	13	13	12	12	11	11	10

*Taken from AM. HEART J. 10: 497, 1935.

from a positive T wave to a flat or inverted T wave. Also, a change from a previously inverted T wave to a flat or upright T wave is abnormal. The RS-T depressions and T-wave inversions are the changes commonly observed. Occasionally, multiple premature beats, widening of the QRS, deep Q waves, prolongation of the P-R interval, or heart block may occur, and these are considered an abnormal response

TABLE III

INCIDENCE OF SIGNIFICANT ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE

	AMOUNT OF EXERCISE			
	STANDARD TWO-STEP TEST		DOUBLE STANDARD TWO-STEP TEST	
	No.	% Positive	No.	% Positive
1. Normal adults over 40 years of age	65	0	34	0
2. Patients with angina pectoris and normal control E.C.G.	54	10 (19%)	41	16 (39%)
3. Patients with angina pectoris and abnormal control E.C.G.	29	15 (52%)	15	10 (67%)
4. Patients with previous coronary occlusion and normal control E.C.G.	10	0	7	1 (14%)
5. Patients with previous coronary occlusion and abnormal control E.C.G.	43	20 (47%)	15	7 (47%)



Fig. 1.—Photograph illustrating technique of standard two-step test.

to the test. In ascertaining the level of the RS-T segment, the P-R segment is considered the isoelectric level. In this report we present the results of performing the tests on 65 normal adults over forty years of age, 83 patients with angina pectoris caused by coronary artery disease, 54 of whom had a normal control electrocardiogram, and 53 patients with previous coronary occlusion, 10 of whom had a normal control electrocardiogram (Table III).

RESULTS

Group 1, Normal Adults.—Sixty-five normal subjects, comprising 58 males and 7 females from forty to sixty-eight years of age, were chosen as controls. They were considered normal in that they appeared healthy,

had no complaints, and were engaged in regular activities. Their physical examination, electrocardiogram, teleroentgenogram, fluoroscopic examination, roentgenkymogram, and exercise tolerance tests were entirely negative.

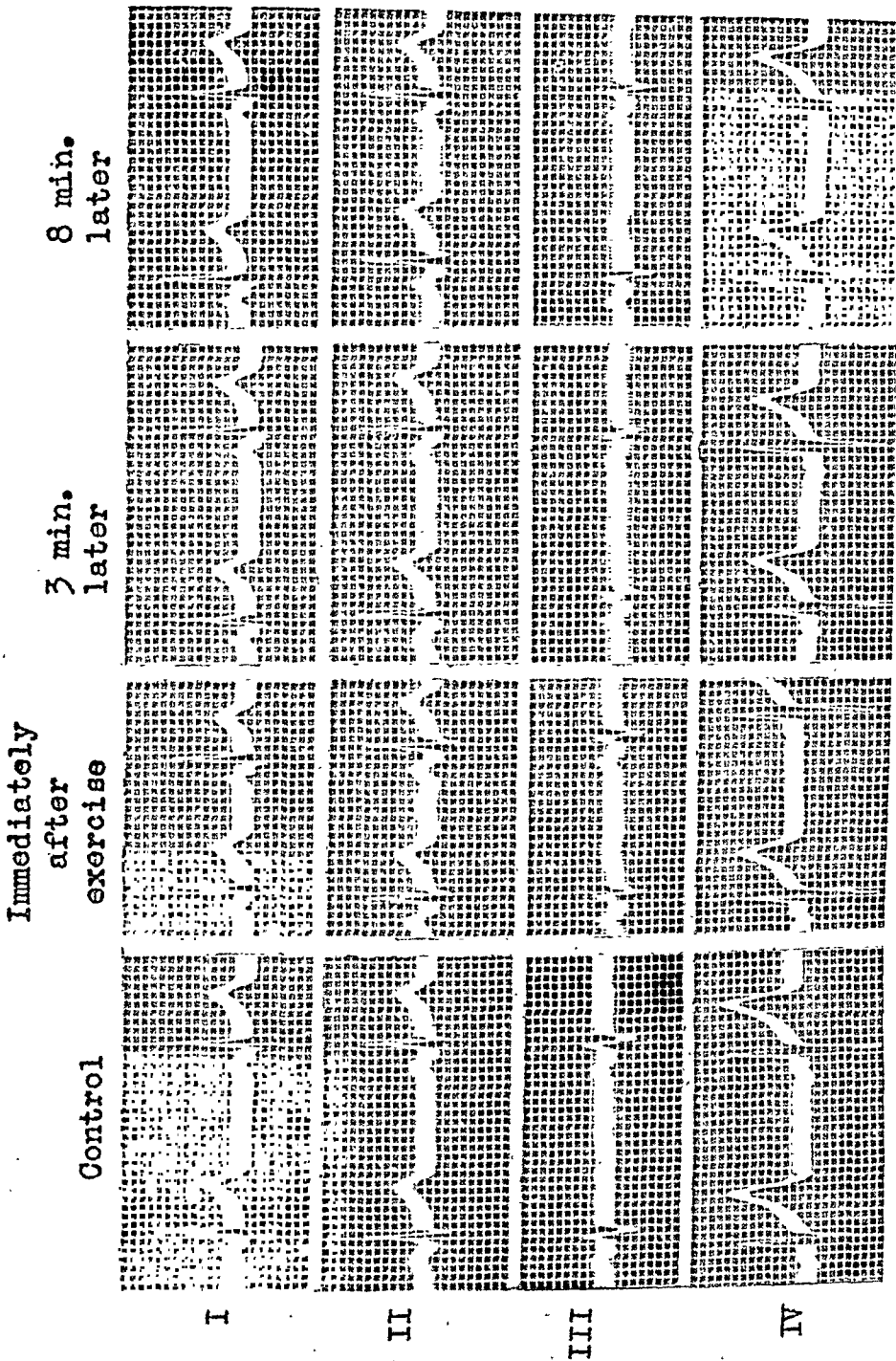


Fig. 2.—A normal man (L. H., 47 years of age. Electrocardiograms after the double standard two-step test (42 trips in 3 minutes) show no change from the normal control record.

These 65 normal persons showed no significant changes in the electrocardiogram after the two-step exercise. In 34 instances we were able to repeat the test with double the number of climbs. In all these, too, there

was a negative response in the electrocardiogram (Table III). In not a single case of our normal series were there changes similar to those observed in the other groups. A negative test is illustrated in Fig. 2, in which are shown the electrocardiograms after a double two-step test (42 trips) on a healthy physician (L. H.), 47 years of age.

Group 2, Angina Pectoris With Normal Electrocardiogram.—This group consisted of 54 patients with angina pectoris whose electrocardiograms were normal. After the standard two-step test, 19 per cent developed significant electrocardiographic changes, and, after the double two-step test, this rose to 39 per cent (Table III). Two illustrative cases are presented.

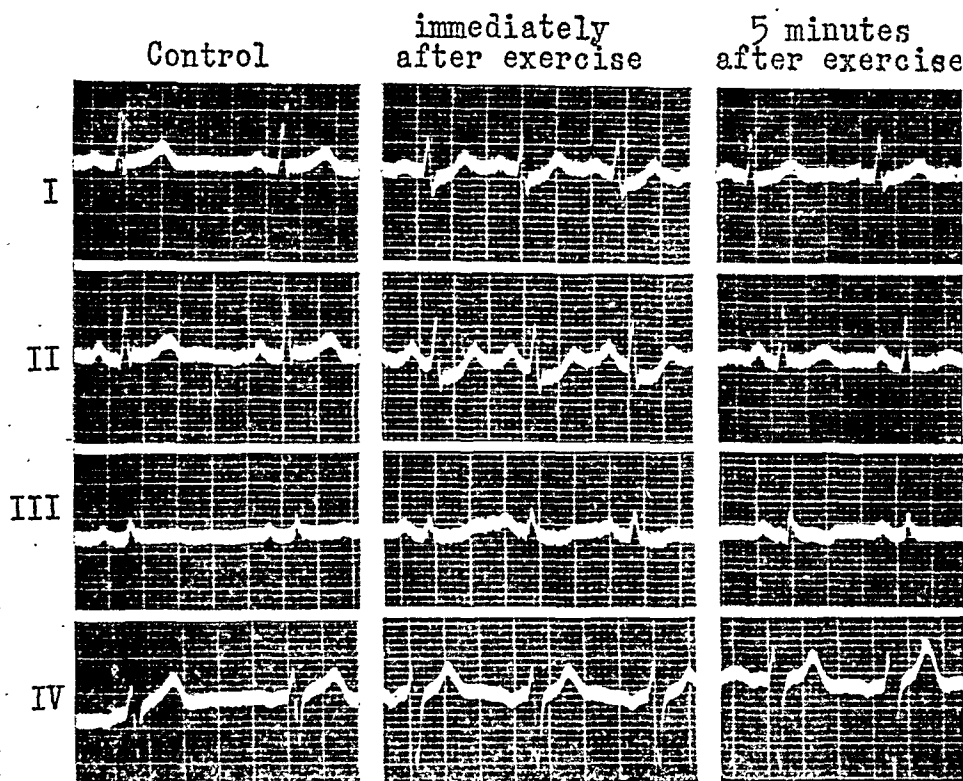


Fig. 3.*—Case 1 (M. K.). A man of 57, suffering from angina pectoris. The control electrocardiogram is normal. After the standard two-step test (20 trips in $1\frac{1}{2}$ minutes) there is transient depression of the RS-T segment in all leads, particularly Leads I and II.

CASE 1 (Fig. 3).—This patient (M. K.), a man, 57 years old, was first seen December 15, 1939, because of pressure in the chest and both arms which was unrelieved by nitroglycerine. The patient weighed about 128 pounds. The heart beat was regular and the rate was 76 per minute; the heart sounds were of good quality and no murmurs were heard. The teleoroentgenogram revealed that the heart and aorta were normal in size, shape, and position. Fluoroscopic examination disclosed good cardiac contractions. The electrocardiogram was entirely normal. The patient had been operated upon for a gastric ulcer in 1930, and an exploratory operation had been performed in 1937 in a search for gastric or intestinal abnor-

*We thank the Journal of the Mount Sinai Hospital (7: 629, 1941) for permission to reproduce this illustration.

malities. Because of the persistence of pain in the chest despite the absence of objective evidence of heart disease, and because it was thought that his complaints might be reflex manifestations of gastrointestinal disease, the patient was admitted to the Mount Sinai Hospital Jan. 4, 1940, for further study.

In the hospital, also, the physical examination, teleoroentgenogram, fluoroscopic examination of the heart, and electrocardiogram were normal. Radiographic investigation of the gastrointestinal tract revealed no abnormalities. The exercise tolerance

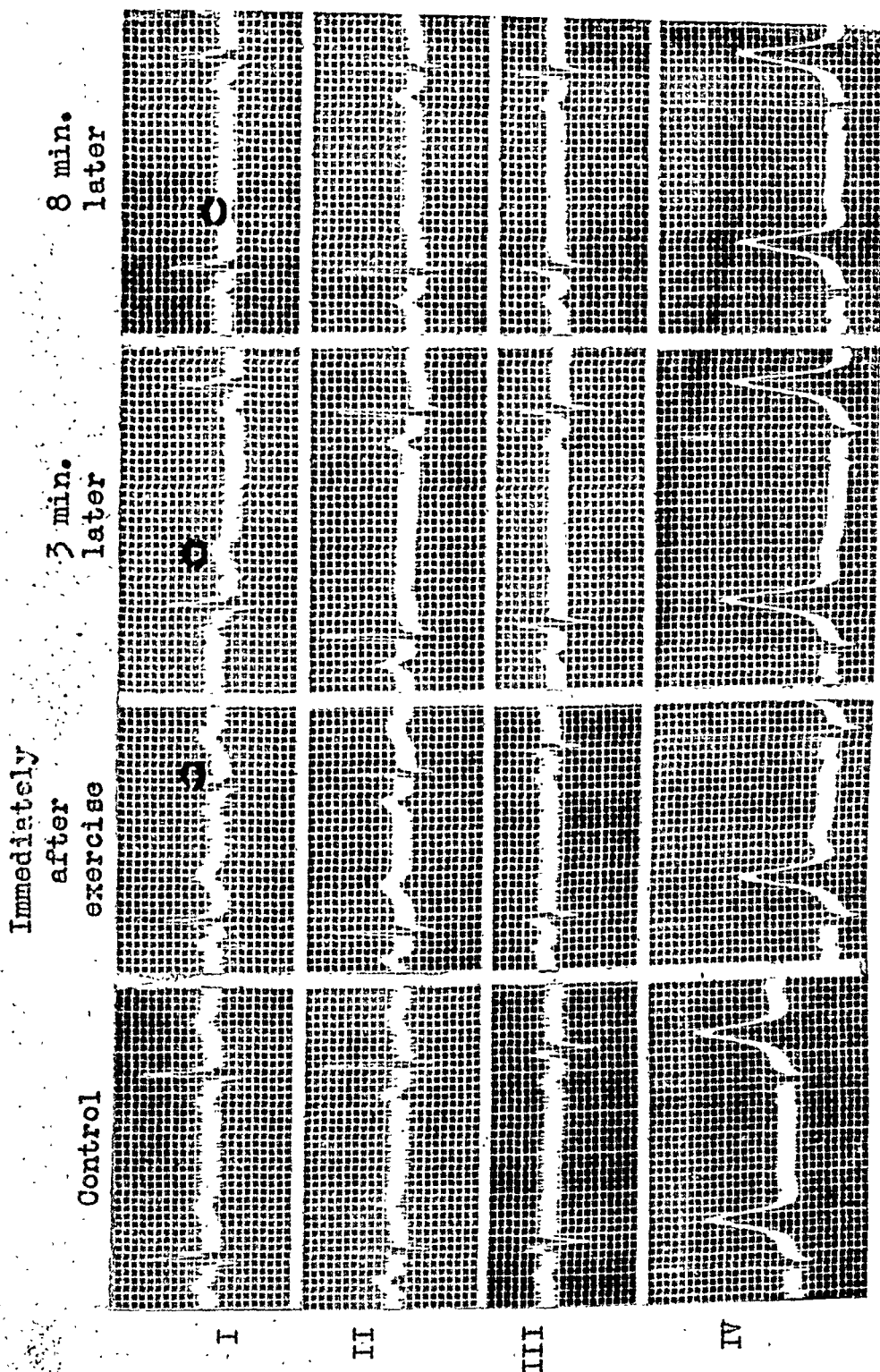


Fig. 4A.—Case 2 (J. G.), male, aged 61 years. Angina pectoris for eleven years. Control electrocardiogram shows left axis deviation, small Q_1 , and slight slurring of QRS. After standard two-step test (21 trips in $1\frac{1}{2}$ minutes) S-T₂ and S-T₃ become depressed, T₂ low, and T₁ higher and pointed.

test, however, showed that the blood pressure and pulse rate failed to return to normal after the standard two-step exercise. Electrocardiograms after standard and double standard exercise were also definitely abnormal, in that they showed distinct depression of the RS-T segments (Fig. 3). The diagnosis of angina pectoris caused by coronary sclerosis was therefore made, and the patient was discharged

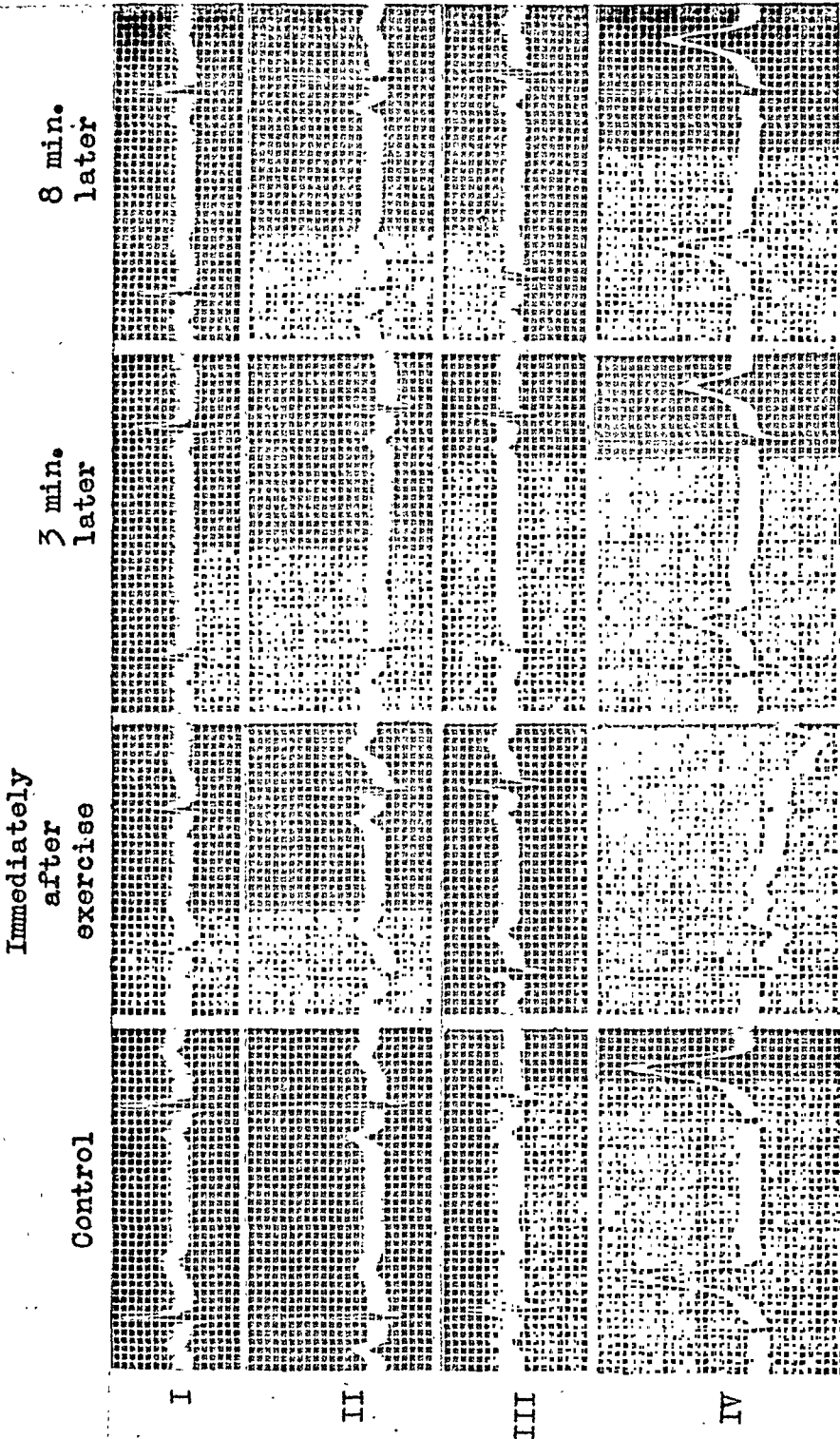


Fig. 4B.—Same case. After double standard two-step test (42 trips in 3 minutes) there is more distinct depression of S-T₂ and S-T₄; T₁ and T₂ become diphasic, and T₃ and T₄ isoelectric. All the changes disappeared within 8 minutes.

Jan. 14, 1940. Aside from the reduced exercise tolerance, the appearance of significant electrocardiographic changes after standard exercise was the only objective sign of organic heart disease. This diagnosis was entirely correct, for the patient died in September, 1940, of acute coronary occlusion.

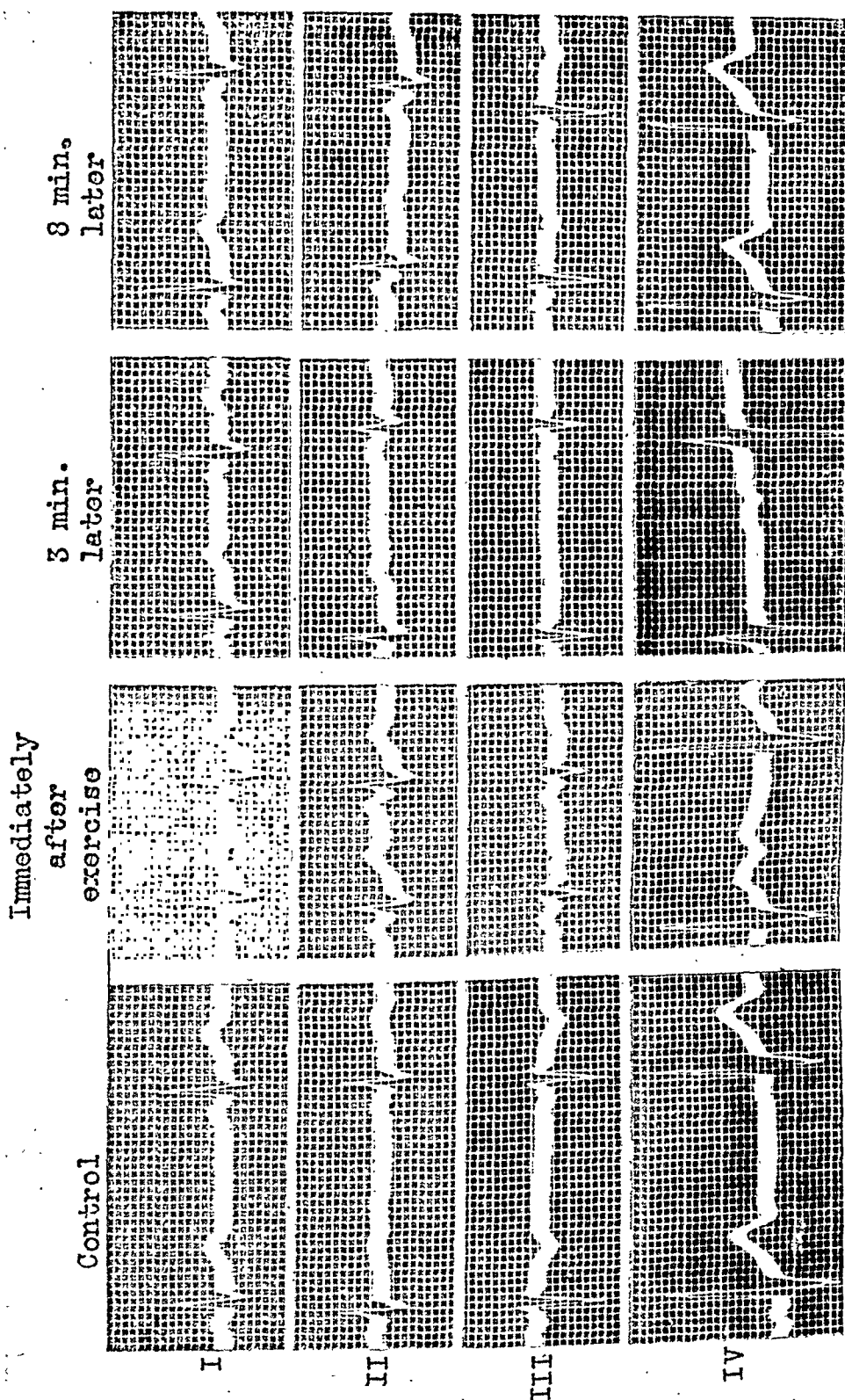


Fig. 5.—Case 3 (M. P.), a man 62 years of age, with angina pectoris. The control electrocardiogram is slightly abnormal, showing left axis deviation, slurring of QRS, a low T_w, and an inverted T_w. After the double standard two-step test (34 trips in 3 minutes) depression of the S-T segment in Leads I, II, and IV, and lowering of T_w appear and last for several minutes.

CASE 2.—Fig. 4*A* shows the electrocardiograms of a 61-year-old man (J. G.) who, because of angina pectoris on effort for the preceding eleven years, had been forced to stop work. The heart sounds were distant and the aorta tortuous, dense, and calcified. However, the size of the heart was normal and the cardiac pulsations were of good amplitude. The electrocardiogram was essentially negative, except perhaps for the presence of a small Q_1 . Immediately after 21 climbs in one and one-half minutes (Fig. 4*A*), RS-T₁ was lowered from an elevation of 1 mm. above the isoelectric line in the control record to a depression of 1 mm. below. Three minutes later T₂ became flat; eight minutes after the exercise the electrocardiogram had returned to normal. When the test was repeated with double the number of trips, i.e., 42 trips in three minutes (Fig. 4*B*), the changes in the electrocardiogram were much more marked. The RS-T segment in both Leads II and III were depressed, and T₄ was inverted immediately after exercise. Three minutes later T₁ was slightly inverted and T₂ flat, but the RS-T abnormalities had disappeared. Eight minutes later the electrocardiogram was again entirely normal. In this case also, therefore, the abnormal electrocardiographic response to standard exercise correlated well with the history that the patient was ill and incapacitated. This case also revealed that double the amount of exertion produces more marked electrocardiographic changes than the standard two-step test.

Group 3, Angina Pectoris and Abnormal Electrocardiogram.—Of the 26 patients with angina pectoris whose control electrocardiograms were abnormal, changes were observed in 50 per cent after the standard number of climbs and in two-thirds after double the standard number of trips (Table III). The test in this group was therefore positive more frequently than among the patients of Group 2, who had normal control electrocardiograms.

CASE 3.—Fig. 5 shows the electrocardiograms of a man (M. P.), 62 years of age, who was suffering from angina pectoris caused by coronary disease. The pain often occurred at rest, as well as on effort, and was sufficiently severe to prevent work. A mild, transient hypertension, slight left ventricular enlargement, and distant heart sounds were the important points in the clinical examination. The electrocardiogram was somewhat abnormal, i.e., QRS measured 0.10 to 0.11 second, T₂ was small, and T₃ was inverted. Significant transient abnormalities appeared after exercise. After the double two-step test, i.e., 34 ascents in three minutes, the RS-T segment in Leads I and II became depressed at least 1 mm. below the isoelectric level, and T₄ became smaller. Three minutes after the exercise, T₄ was flat. Here again the abnormality in the electrocardiogram after the exercise correlates well with the known clinical facts, i.e., severe subjective symptoms with an only slightly abnormal control electrocardiogram.

Groups 4 and 5, Previous Coronary Occlusion.—The 53 patients who had had acute coronary artery occlusion previously were also divided into two groups: 10 whose electrocardiograms after the attack had become normal, and 43 whose tracings remained abnormal. In the first group, whose cardiac function was better, there were no positive results with the standard two-step test, and only one patient gave an abnormal response after the double exertion (Table III). Of the second, larger group with abnormal electrocardiograms, almost one-half showed a positive response to the standard and double two-step exercise. Thus, in this group, also, the electrocardiogram after exercise correlates with the pa-

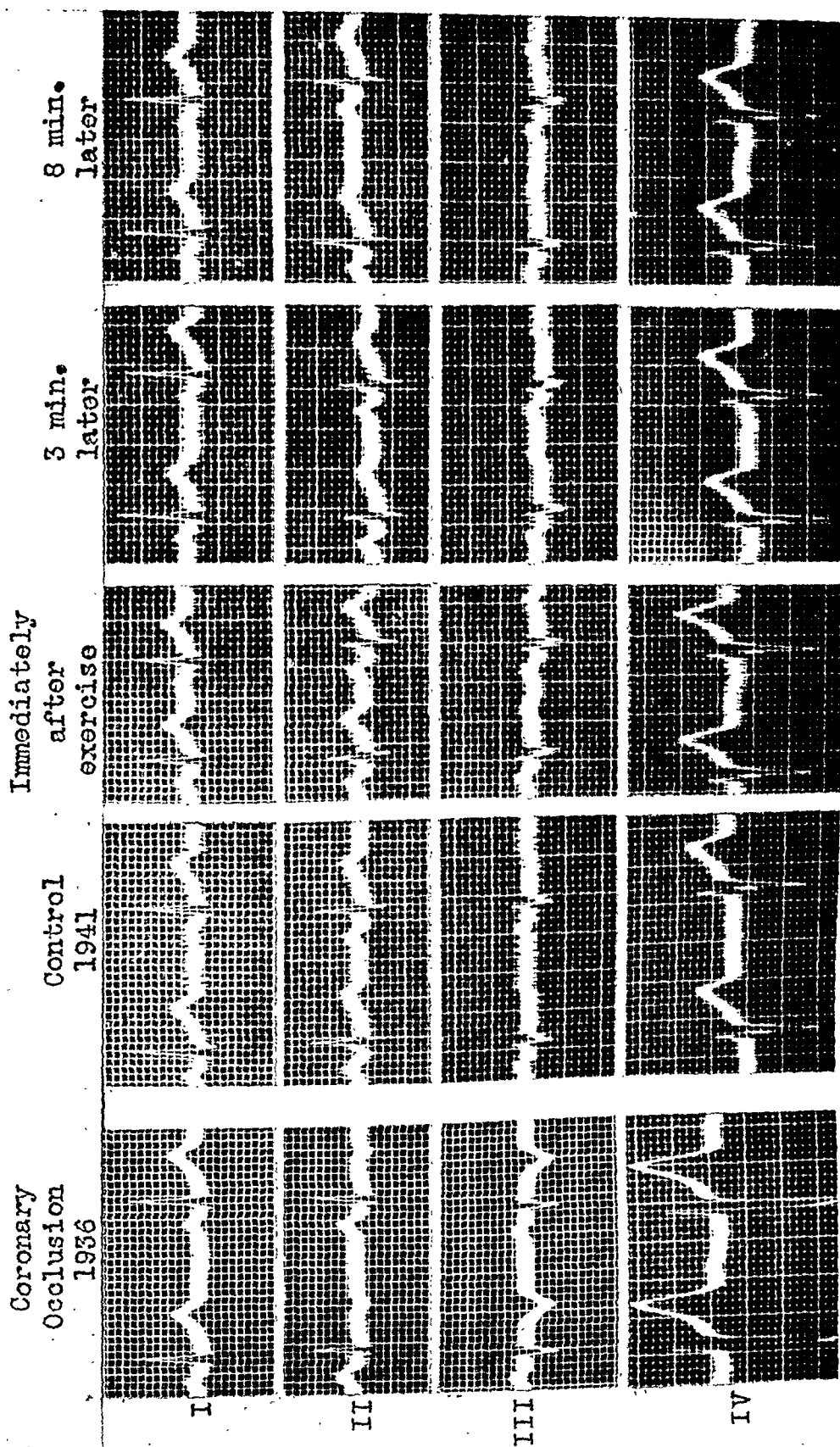


Fig. 6.—Case 4 (F. C.), a man 40 years of age, who had acute coronary occlusion five years earlier and made a complete recovery. Electrocardiogram in 1936 shows inverted T_s and T₄. Control record in 1941 is normal. No changes occurred after the double standard two-step test (42 trips in 3 minutes).

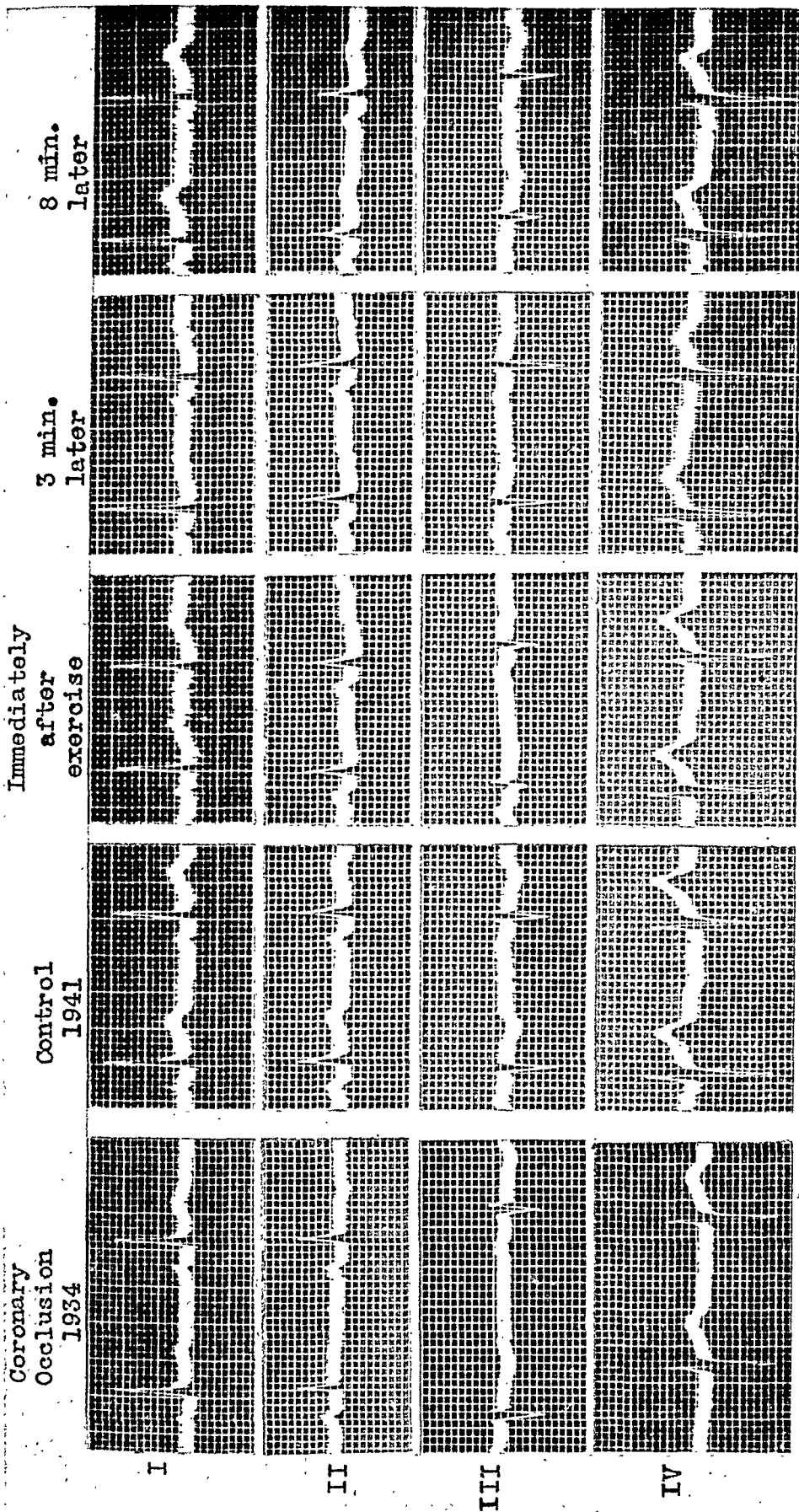


Fig. 7.—Case 5 (P. G.), a man of 60 who had acute coronary occlusion 7 years before; since then he has had moderately severe angina pectoris. Electrocardiogram in 1934 shows semi-inverted T_2 and T_3 . Control record in 1941 is normal except for T_3 inversion. After the double standard two-step test (38 trips in 3 minutes) S- T_1 and S- T_2 are slightly depressed, and T_1 and T_2 semi-inverted.

tient's cardiac function; the changes are more pronounced when function is known to be poor. In the following cases the electrocardiogram returned to normal after coronary occlusion.

CASE 4.—In the first case, that of a man of 40 (F. C., Fig. 6), even a double two-step test produced no significant changes in the electrocardiogram. This was not unexpected, for, although the patient had had acute myocardial infarction in 1936 (five years earlier), he had made a complete recovery; he was entirely asymptomatic and the cardiac function was normal as judged clinically and by laboratory study. He was working full time at his old occupation as a salesman without any difficulty at all. The size of the heart, heart sounds, electrocardiogram, cardiac pulsations, and exercise tolerance test were entirely normal. No evidence of coronary insufficiency could be elicited, even by the double two-step test.

CASE 5.—Fig. 7 shows the result of the test on a 53-year-old man (P. G.) who had had acute coronary occlusion seven years before. He was a large, hyposensitive man, a doorman who could not work because of pain on effort. Although the electrocardiogram had returned to normal, other clinical signs of coronary insufficiency persisted. The exercise tolerance test (blood pressure and pulse rate reactions) was below average, and pain in the chest occurred during the test. Clinically he was considered an ill man, in spite of the normal electrocardiogram. After the double two-step exercise, the electrocardiogram became definitely abnormal; semi-inversion of T_1 and T_2 appeared. This case also demonstrates the correlation of the test with the patient's history.

CORRELATION OF ELECTROCARDIOGRAM WITH BLOOD PRESSURE AND PULSE RATE AFTER EXERCISE

The cases reported above have given evidence that the character of the electrocardiogram after standard exercise is a good measure of cardiac function. Further evidence is obtained by comparing the results of this test with those of the ordinary exercise tolerance test. These are presented in Table IV. The exercise tolerance in the normal control group and in the cases of angina pectoris was ascertained by the blood pressure and pulse rate reaction to the standard two-step exertion. Repeated blood pressure and pulse rate readings were recorded until basal levels were attained.² Then the patient made the number of trips required for his age and weight in exactly a minute and a half. Within two

TABLE IV

CORRELATION OF CARDIAC FUNCTION, AS ASCERTAINED BY BLOOD PRESSURE AND PULSE RATE RESPONSE TO TWO-STEP TEST, WITH ELECTROCARDIOGRAPHIC RESPONSE TO STANDARD EXERCISE

Group	Cardiac Function	STANDARD TWO-STEP TEST		DOUBLE STANDARD TWO-STEP TEST	
		No. of Cases	% Positive	No. of Cases	% Positive
1. Normal adults	Good	65	0	30	0
	Poor	0	0	0	0
2. Anginal pectoris with normal control E.C.G.	Good	25	12	18	22
	Poor	27	19	18	44
3. Angina pectoris with abnormal control E.C.G.	Good	4	25	3	33
	Poor	21	62	10	90

minutes after cessation of the exercise, the blood pressure and pulse rate should return to within ten points of the resting (basal) figures. Otherwise, the exercise tolerance was considered poor or below average.² It is necessary to have the patient always turn toward the examiner at the beginning of a reascent. (This meant always turning in a different direction, so that dizziness and the resulting changes in blood pressure were prevented.)

In the healthy controls (Group 1), the exercise tolerance was uniformly good and the electrocardiograms always remained normal (Table IV). In the angina pectoris group with normal control electrocardiograms (Group 2), there was a distinctly larger percentage of abnormal electrocardiographic responses among those with poor exercise tolerance, as compared to those with a normal tolerance; the respective percentages were 12 per cent, compared with 19 per cent, and 22 per cent, compared with 44 per cent, depending on whether the standard or doubled two-step exercise was utilized (Table IV). In the group of patients who had angina pectoris and abnormal control electrocardiograms (Group 3), the percentage of abnormal electrocardiographic responses after the two-step exercise was again larger among those with poor cardiac function than among those with normal cardiac function, as measured by the blood pressure and pulse rate response. After the standard two-step exercise the incidence of abnormal electrocardiographic changes in those with normal cardiac function was 25 per cent, and, in those with poor cardiac function, it was 33 per cent. Similarly, after the double two-step exertion, the percentages were 62 and 90, respectively (Table IV).

CHARACTER OF ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE

Table V summarizes the changes in the four leads of the electrocardiograms of patients with the anginal syndrome. Similar abnormalities were observed in the other groups of patients. RS-T depression of more than $\frac{1}{2}$ mm. below the isoelectric level in any lead was the most frequent abnormality encountered. It was found most commonly in Leads I and II. This applied also to T-wave changes, which were less frequent than RS-T depression. In other words, the limb leads were abnormal oftener than the chest lead, but all leads were helpful. Occasionally the precordial lead showed abnormalities when there were none in the standard limb leads.

TABLE V

INCIDENCE OF ELECTROCARDIOGRAPHIC CHANGES (RS-T AND T WAVE) IN DIFFERENT LEADS AFTER EXERCISE IN PATIENTS WITH ANGINA PECTORIS

	Lead I	Lead II	Lead III	Lead IV
1. Angina pectoris with normal control electrocardiogram	19	22	4	12
2. Angina pectoris with abnormal control electrocardiogram	21	21	1	8

DISCUSSION

A great deal has been written on the subject of the electrocardiogram after exercise, and a review of the literature will be found in the papers of Feil⁵ and Riseman, Waller, and Brown,¹⁰ which should be consulted. It is essential that a standard amount of exercise be performed, for many authors⁵⁻¹⁰ have shown that excessive work may produce significant electrocardiographic changes in normal persons. That is why we used the standard or double two-step tests, which produce no significant electrocardiographic changes in normal persons. When definite alterations appear in the electrocardiogram after the two-step exercise test, the patient is not normal. In our experience the test has proved to be of practical value. At times, the electrocardiogram after standard two-step exercise may be abnormal when physical and laboratory examination is entirely negative (Case 1). It is to be remembered, however, that the test is significant only when it is positive, that is, when electrocardiographic changes occur after standard exercise. Not every patient who has organic heart disease, whether it be coronary sclerosis, syphilitic aortitis, or aortic insufficiency, gives a positive response. Therefore, the absence of electrocardiographic changes after standard exercise does not rule out the presence of organic heart disease.

The electrocardiographic changes which occur after exercise, namely, depression of the RS-T segment and lowering or inversion of the T wave, are similar to those which occur with a spontaneous attack of angina pectoris^{5, 10} or in acute coronary insufficiency^{11, 12} caused by hemorrhage, shock, heart failure, or tachycardia. They are more transient than the changes observed in the latter conditions. They are due to the anoxemia of the myocardium which results from a discrepancy between the coronary blood flow and the increased demand of the myocardium for oxygen. In other words, the exercise induces a transient coronary insufficiency which is relieved in a few minutes by rest. The electrocardiographic changes are also similar to those caused by generalized anoxemia.¹³⁻¹⁵

We have never observed any significant elevation of the RS-T segment after exercise, although occasional instances have been reported by several authors.^{6, 16, 20} It must be extremely uncommon, however. The changes after exercise are not like those of acute coronary artery occlusion, for no Q waves appear, and, with the exception of the above quoted isolated cases, elevation of RS-T and a reciprocal relation between Leads I and III do not occur. As already stated, the changes which do appear are typical of acute coronary insufficiency, but not of coronary occlusion.

The two-step test is a simple, quantitative one. It is without danger, and utilizes exercise to which everyone is accustomed, no matter how sedentary his work is. We have never seen pain develop in normal subjects, and this has also been the experience of Feil.⁵ If pain develops in

a case of coronary artery disease, the test can be continued, provided the pain is not severe. Even the presence of pain may not affect the results.

It is possible to perform the two functional tests of the heart at once, that is, one can record the electrocardiogram as well as the blood pressure and pulse rate after the standard exercise. The combined test should preferably be performed by two persons; one records the electrocardiograms and the other obtains the blood pressure and pulse rate readings, but, with training, one person can record the electrocardiogram within one minute and the blood pressure and pulse rate during the next minute. The two tests are better than one in evaluating cardiac function or as aids in making a diagnosis. Prognosis, too, should not be judged by one test alone, but by utilizing all possible observations.

The changes in the electrocardiogram usually last only a few minutes, rarely more than eight to fifteen minutes. Occasionally they disappear within one minute after cessation of the exercise. This emphasizes the importance of recording the first electrocardiogram as quickly as possible after the exercise. The electrodes are therefore kept strapped to the patient's arms and leg while he climbs the steps, so that the electrocardiogram can be taken the moment the climbs are finished (Fig. 1).

The P-R segment was chosen as the isoelectric level only after considerable experimentation. In electrocardiograms in which the heart rate was rapid, it was found that the P-R segment was the only portion of the curve in which the level remained unchanged. Naturally, after exercise, the heart beat is accelerated and diastole (represented by the T-P interval) is shortened. The T-P segment remains elevated because there is insufficient time for it to reach its true isoelectric level before the next beat. The RS-T segment will then show an apparent depression below the T-P segment. Furthermore, a U wave often appears after exertion, or may have already been present, and this, also, elevates the T-P segment above its correct isoelectric level. If one carefully examines the electrocardiogram when the heart rate is slow, it will be seen that the T-P segment nearly always slants downward slightly and reaches its lowest level after a long diastole. The lowest level is always the same as the P-R level. When the heart rate is increased, the T-P segment is shortened and fails to reach the true isoelectric line. Riseman, Waller, and Brown¹⁰ also used the P-R level as the isoelectric level with which to compare the changes in the RS-T segment after exercise. A depression of the RS-T segment of only 0.5 mm. would at first appear to be insignificant and insufficient as a criterion of abnormal response to exercise. However, we have found that if the P-R segment is used as a control, a depression of more than 0.5 mm. never occurs in normal persons.

We have described two variations of the test for electrocardiographic changes after exercise, namely, one based on the standard amount, and the other on double that amount, of two-step exercise. The former, which is less strenuous and is completed in one and one-half minutes,

should be used for patients who are known to have, or suspected of having, some impairment of the heart. It is thus indicated for those with the anginal syndrome and those who have had previous attacks of coronary occlusion, coronary insufficiency, or paroxysmal dyspnea, and in the presence of valvular, syphilitic, or congenital heart disease. It should prove of value also in annual physical examinations and examinations for retirement. The electrocardiogram after double the standard two-step exercise, i.e., exertion for three minutes at a standard rate, may be used for testing military recruits, young and middle-aged persons, or any patient in the previously mentioned groups whose electrocardiogram after standard two-step exertion has remained normal. Anyone with a normal or practically normal electrocardiogram should have this double exertion test. In hundreds of tests with the double two-step exercise we have never seen any harmful or really painful result. Of course, this somewhat more strenuous exercise test should not be used on a patient who is acutely ill or when an acute illness is just subsiding. As a general rule, subjects 50 years of age or older should be subjected to the standard test first.

SUMMARY AND CONCLUSIONS

1. A new modification of a test of heart function is described; it utilizes the effect of a definite amount of work on the electrocardiogram. The work consists of the two-step exercise tolerance test, employing the standard number of climbs or double that number. By this method the exertion is limited to a definite amount, and is standardized for the patient's age, sex, and weight.

2. No significant electrocardiographic changes after these tests have been observed in normal persons. Depression of the RS-T segment more than 0.5 mm. below the P-R segment or flattening or inversion of the T wave is abnormal, and is indicative of coronary insufficiency.

3. Changes were observed after the standard test in one-fifth of the cases of angina pectoris with normal control electrocardiograms, and in two-fifths after the double test; of the cases in which the control electrocardiogram was abnormal, they occurred in one-half after the standard test and in two-thirds after the double test.

4. The RS-T and T-wave changes occurred most commonly in Leads I and II and disappeared within eight minutes. They were similar to those caused by anoxemia and acute coronary insufficiency.

5. The test is particularly useful in studying patients with symptoms of heart disease when other methods of examination, including the electrocardiogram, are negative. A negative test does not exclude the presence of organic heart disease.

6. Correlation of the results of the test with the patient's clinical status, as ascertained from symptoms, cardiac examination, and the exercise tolerance test, has shown that the test is a good measure of cardiac function.

7. The test is simple to perform, is not dangerous except for very ill patients, and is useful in diagnosis, prognosis, and in following the patient's progress. It can be combined with the exercise tolerance test; i.e., the pulse rate and blood pressure, as well as the electrocardiogram, can be recorded after the standard exercise. The electrocardiographic, pulse rate, and blood pressure responses to standard and double exercise are useful as cardiac fitness tests in military and aviation medicine.

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HYPOPLASIA OF THE AORTA WITHOUT TRANSPOSITION WITH ELECTROCARDIOGRAPHIC AND HISTOPATHOLOGIC STUDIES OF THE CONDUCTION SYSTEM

MAURICE LEV, M.D., AND SAMUEL T. KILLIAN, M.D.
CHICAGO, ILL.

THERE are a number of anomalies of the heart which include hypoplasia of the aorta. These may be classified as follows:

- (1) Hypoplasia of the aorta associated with transposition;
- (2) Hypoplasia of the aorta not associated with transposition,
 - (a) with aortic and/or mitral stenosis or atresia,
 - (b) without mitral or aortic stenosis or atresia.

In a series of fifty congenitally malformed hearts studied by one of us (M. L.) at the Michael Reese Hospital, hypoplasia of the aorta was present in 20 per cent. However, it was associated with mitral or aortic atresia in only three cases. The subject has been dealt with recently by Evans,¹ Roberts,² McNerney,³ Abbott,⁴ Monserrat,⁵ Rukstinat,⁶ Lippincott,⁷ von Haam and Hartwell,⁸ Baggenstoss,⁹ and Anderson and Sano.¹⁰

Electrocardiographic studies of congenital aortic atresia and stenosis have been reported in only one instance.¹⁰ Histologic studies of the conduction system in congenitally malformed hearts are few.¹¹ The present report deals with both studies in two cases.

CASE 1.—

History.—This male child was born July 30, 1940; it was a normal delivery. The duration of gestation was 8 months. The birth weight was 2460 grams, and the child measured 46 cm. in length. At birth the infant was moderately cyanotic, and the cyanosis increased during the first day as its condition became worse. The respirations were rapid and shallow. Bronchial breathing and râles were heard at the bases of both lungs. There was a short systolic murmur over the precordial area, and the pulmonic second sound was accentuated. The liver was palpable two fingerbreadths below the right costal margin. On the second day of life the cyanosis became more marked, the abdomen became distended, vomiting occurred, and there was twitching of the left side of the face and left arm and leg. Treatment consisted of oxygen, gastric lavage, vitamin K intramuscularly, fluids subcutaneously, and stimulants. These were of no avail, however, and the child died forty-four hours after birth.

A roentgenogram of the chest (Fig. 1) was read as follows: "The superior mediastinum is widened, with the lateral walls almost vertical. The findings suggest an enlarged thymus. The heart shadow is large and globular, with the bulk of the heart to the left of the midline. This finding would suggest the possibility of a congenital heart. The lung field markings in the right lower, and the left mid-lung field, are exaggerated."

From the Pathology and Cardiovascular Departments, Michael Reese Hospital, Chicago.

Aided by the A. D. Nast Fund for Cardiac Research, and the Joseph G. Snyder Fund.

Received for publication May 4, 1942.

An electrocardiogram (Fig. 2) revealed the following: "Rate is 107. P-R interval is 0.16 second. QRS₁ is M-shaped, mainly inverted, and tiny. QRS₂ and QRS₃ are upright, slurred, and small. QRS duration is 0.14 second. T₁ and T₂



Fig. 1.—Roentgenogram of chest in Case 1. Note the large and globular shaped heart, especially prominent in the left side of the chest. Described in text.

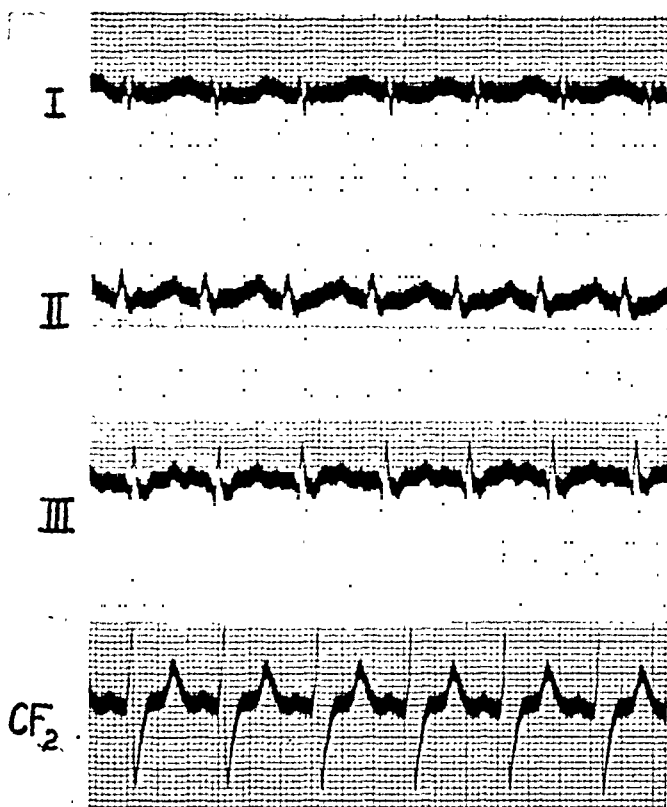


Fig. 2.—Electrocardiogram in Case 1. Described in text.

are small. Lead CF_2 is normal in configuration but there is prolongation of the P-R interval and the QRS duration. Interpretation: Sinus rhythm. First degree auriculo-ventricular block. Intraventricular block of the indeterminate type with low 'voltage.' Definitely abnormal curve."

Clinical Diagnosis.—Congenital heart disease, with circulatory insufficiency. Extensive, fulminating bronchopneumonia. Pulmonary atelectasis. Possibly cerebral hemorrhage.

Post-Mortem Examination.—Aside from the abnormalities in the heart, the pathologic diagnoses were: (1) prematurity; (2) subarachnoid hemorrhage; (3) pin-point intracerebral hemorrhages; (4) hemorrhages into both kidneys; (5) partial pulmonary atelectasis; (6) hyperemia of all the organs.

Heart.—(Figs. 3 and 4). The heart was triangular in shape. The apex was formed by the right ventricle. From the base of the heart two vessels emerged: a large one situated to the left and somewhat anteriorly, and a small one situated to the right and somewhat posteriorly. The mutual relationships of the various heart chambers were normal.



Fig. 3.



Fig. 4.

Fig. 3.—Anterior view of the heart in Case 1. Note the hypoplastic aorta and large pulmonary artery; A, aorta; P, pulmonary artery.

Fig. 4.—Left auricular and ventricular view of the heart in Case 1. Note the hypoplastic left ventricle; L, left ventricle.

The right auricle was markedly dilated and its wall was relatively thickened; the latter measured as much as 1 mm. in thickness. The superior and inferior venae cavae and coronary sinus entered this chamber normally. The Eustachian and Thebesian valves formed one curtain guarding the inferior vena cava and the coronary sinus. The limbus in its upper portion was well formed but was deficient in its anteroinferior portion. The septum primum was well formed. There was no anatomic unity between the septum primum and the limbus; this produced a directly patent foramen ovale, the diameter of which was 5 mm.

The tricuspid orifice measured 4.3 cm. in circumference. The tricuspid valve and its chordae tendineae and papillary muscles were normal.

The right ventricle was markedly enlarged; the thickness of its wall was 1 mm. at the pulmonic orifice, 2 mm. at the tricuspid orifice, and 1 mm. at the left lateral margin. The muscle bundles of the right ventricle were normal in contour. From this chamber emerged the pulmonary artery. This was the large vessel which had been seen externally, to the left and anteriorly.

The pulmonic orifice measured 2.6 cm. in circumference. It was guarded by a normal right cusp and a large cusp situated to the left and anteriorly. The latter cusp was incompletely divided into two parts, a left and anterior portion, by a low band traversing the region of the sinus of Valsalva. The pulmonary artery gave off the right and left branches normally. The ductus arteriosus was widely patent. The muscular interventricular septum was complete. The "pars membranacea," however, was muscular.

The left auricle was relatively small, and its wall was relatively thin. It received the four pulmonary veins normally. The mitral orifice measured 1.3 cm. in circumference. The left auriculoventricular valve consisted of a semilunar band of endocardial tissue which was attached to two greyish-white ridges in the anterior and posterior walls of the left ventricle. These ridges were in the normal position of the anterior and posterior papillary muscles of the left ventricle in the normal heart.

The left ventricle was a minute chamber, and its wall measured as much as 3 mm. in thickness. Its lining was greyish-white, opaque, and thickened. In the region where the normal aorta should have emerged, there was a slight puckering. However, no vessel was seen to emerge from the left ventricle.

The small vessel which emerged externally to the right and posteriorly was the aorta; however, it did not enter the heart. The proximal portion of the aorta ended in an irregularly puckered area at the base of the heart without valvular structure. In this region the right and left coronary arteries emerged. The course and distribution of the coronary arteries were normal. The circumference of the ascending aorta measured 5 mm. The transverse portion of the aorta gave off the brachiocephalic vessels normally. Its circumference measured 8 mm. The transverse aorta united with the ductus arteriosus to form the descending aorta, which measured 8 mm. in circumference.

Histologic studies of the myocardium revealed a marked increase in connective tissue in the myocardium adjacent to the endocardium. The perivascular connective tissue was especially increased about many arteries, the lumens of some of which were narrowed. Also, the endocardium presented a marked increase in connective tissue. This was partially hyalinized and contained small foci of calcium deposits. Both the mitral and tricuspid valves showed an increase in connective tissue. There was no distinct evidence of active inflammation anywhere in the heart.

The Purkinje system was studied by incomplete serial sections stained with hematoxylin and eosin and by the van Gieson method. The auriculoventricular node, the bundle of His, and the left branch were clearly recognizable anatomically. The right branch could not be identified. The auriculoventricular node revealed no pathologic change (Fig. 8). The bundle of His, however, was embedded in a large mass of scar tissue (Fig. 9). Masses of this tissue invaded the bundle, and there was a distinct disruption in continuity of some of its fibers and in the fibers of the beginning of the left branch. In addition, the distal portion of the left branch lay encased in, and was irregularly subdivided by, the markedly increased hyalinized connective tissue in the endocardium of the left ventricle (Fig. 10).

CASE 2.—

History.—This male infant was born June 25, 1937, after a normal full-term pregnancy; the delivery was normal. It weighed 4,215 grams and measured 50 cm.

in length. The mother, aged 22 years, had one other child who was living and well. After birth the child was cyanotic; it died June 27, after having lived forty-five hours.



Fig. 5.—Roentgenogram of chest in Case 2. The heart is enlarged. Described in text.

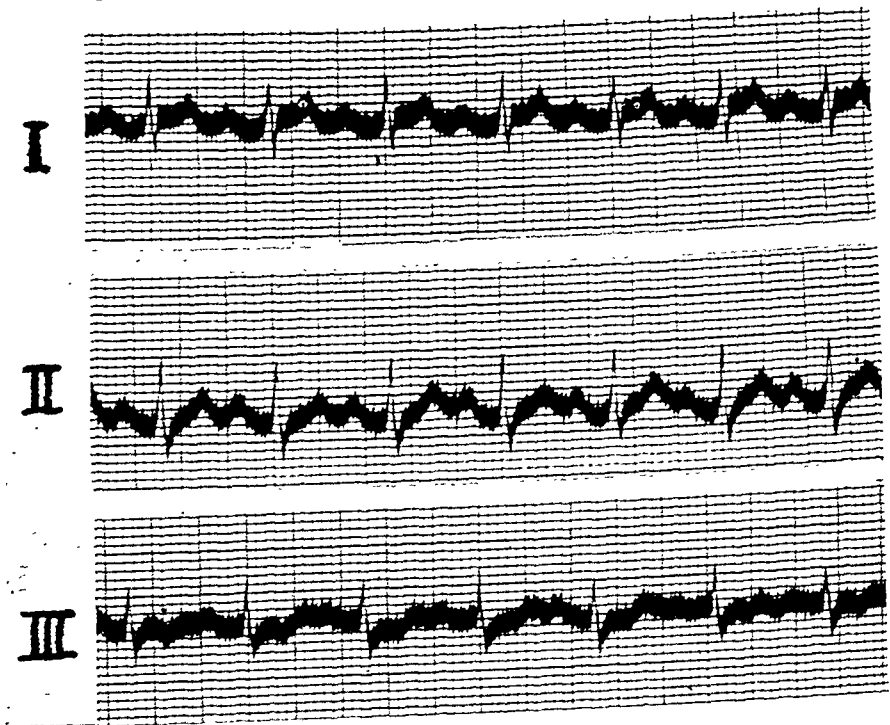


Fig. 6.—Electrocardiogram in Case 2. Described in text.

A roentgenogram of the chest (Fig. 5) showed that the heart outline was larger than normal and rather globular. A haziness involved almost the entire right upper lobe and a portion of the left upper lobe, suggesting atelectasis. No thymus was recognized.

An electrocardiogram (Fig. 6), taken June 27, revealed the following: "Rate is 125. P-R interval is 0.20 second. QRS is up in all leads and small. QRS duration is 0.08 second. S-T₁ and S-T₂ are elevated, and S-T₃ depressed. T₃ is small. Interpretation: Sinus rhythm. First degree auriculoventricular block. Intra-ventricular block of the indeterminate type with low 'voltage.' Definitely abnormal curve."

Post-Mortem Examination.—Aside from the heart, the pathologic diagnoses were: (1) confluent bronchopneumonia; (2) hemorrhages in the lung, thymus, peripancreatic tissue, and mesentery.

Heart.—(Fig. 7). The heart was somewhat enlarged and globular in shape. The apex was formed by the right ventricle. From the base, two vessels were seen to emerge, a larger one anterior and to the left, and a smaller one, posterior and to the right. The mutual relationships of the various heart chambers were normal.



Fig. 7.—Anterior view of the heart in Case 2. Note the hypoplasia of the aorta, the dilatation of the pulmonary artery, and the right ventricular hypertrophy; A, aorta; P, pulmonary artery.

The right auricle was enlarged, and its wall was somewhat thickened. The superior and inferior venae cavae and coronary sinus entered this chamber normally. The Eustachian and Thebesian valves were absent. The limbus (septum secundum) was well formed in its upper portion, but deficient in its lower. It described an incomplete arc, measuring 0.8 cm. in greatest diameter. The septum primum was well formed, and its free edge pointed anterosuperiorly. The septum primum and

secundum were not anatomically united, leaving an obliquely shaped, widely patent foramen ovale which measured 0.6 cm. in greatest diameter.

The right auriculoventricular orifice measured 4.5 cm. in circumference. It was guarded by a valve consisting of two large leaflets, an anterior and a septal. The anterior leaflet had the topography of the normal anterior leaflet of the tricuspid valve, and was connected to a normally formed but thickened anterolateral papillary muscle. The septal leaflet presented numerous chordae tendineae, attached

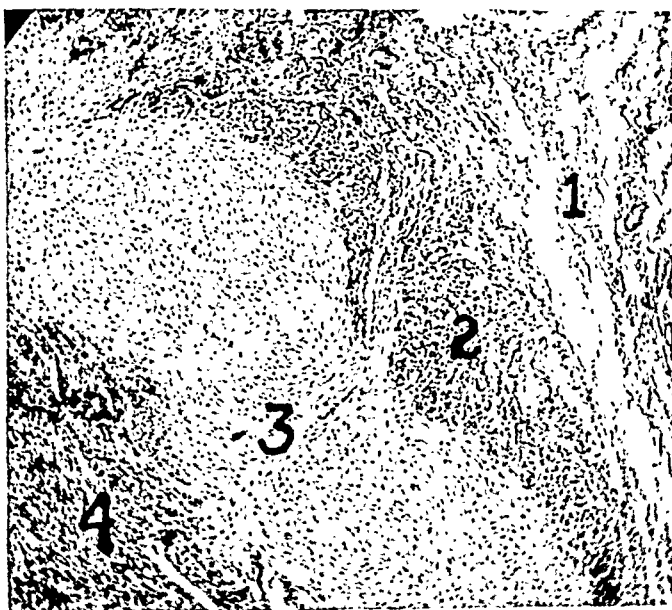


Fig. 8.—The A-V node in the region of the central fibrous body in Case 1. Hematoxylin-eosin preparation, $\times 52$. There is no abnormality; 1, auricular musculature; 2, A-V node; 3, central fibrous body; 4, ventricular musculature.

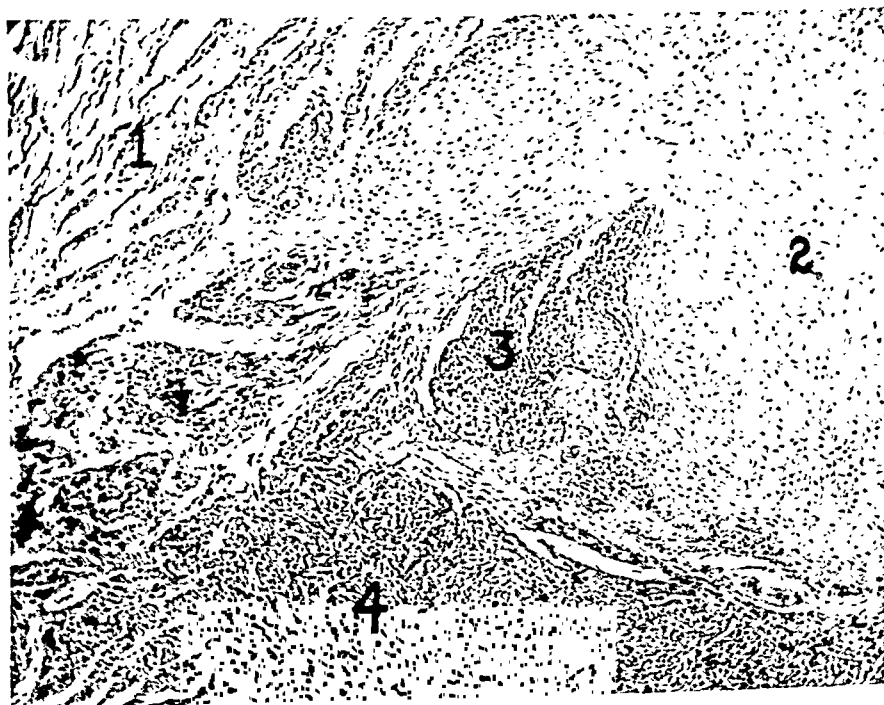


Fig. 9.—The bundle of His in Case 1. Hematoxylin-eosin preparation, $\times 72$. Note the disruption of the bundle as it gives off the left bundle branch; 1, auricular musculature; 2, fibrous tissue at the base of the aortic valve; 3, bundle of His; 4, beginning of left branch.

directly to the trabeculae carneae of the right ventricle. There was no posterior papillary muscle in the right ventricle.

The right ventricle was markedly enlarged and occupied most of the heart. Its wall measured 2 mm. at the left lateral margin. The septal and parietal muscle bundles were normally formed, but thickened, especially the latter. The vessel



Fig. 10.—Portion of the left bundle branch in Case 1. Hematoxylin-eosin preparation, $\times 120$. There are marked degenerative changes in the muscle fibers of the bundle branch as it lies in the markedly thickened and fibrous endocardium. Connective tissue interrupts the continuity of the muscle fibers; 1, ventricular musculature; 2, bundle branch fibers; 3, markedly thickened endocardium.

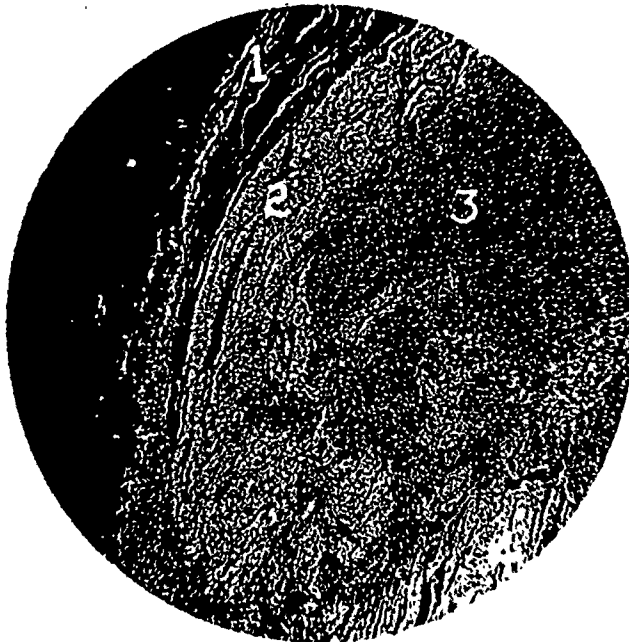


Fig. 11.—The A-V node in Case 2. Hematoxylin-eosin preparation, $\times 40$. There is no abnormality; 1, auricular musculature; 2, the A-V node; 3, central fibrous body; 4, ventricular musculature.

emanating from this chamber was the pulmonary artery. This was the large vessel situated anteriorly and to the left. Its orifice measured 2 cm. in circumference. Its valve consisted of three cusps which were in normal position. The artery gave off the right and left pulmonary branches normally. The ductus arteriosus was widely patent.

The left auricle was small in comparison to the right. It received the four pulmonary veins normally. The left auriculoventricular orifice was correspondingly small and measured 2 cm. in circumference. Its valve leaflets, chordae tendineae, and papillary muscles had the topography of the normal mitral valve.



Fig. 12.—The bundle of His, with its branching, in Case 2. Hematoxylin-eosin preparation, $\times 56$. Note the large mass of connective tissue displacing the muscle fibers of the main bundle; 1, bundle of His; 2, fibrous tissue in the bundle; 3, right bundle branch; 4, left bundle branch; 5, ventricular musculature.

The left ventricle was so small that it appeared almost as an appendage of the right ventricle. Its wall measured 3 mm. in thickness. The muscular interventricular septum was topographically normal. The pars membranacea was replaced by muscle. Emanating from this chamber was the aorta. This was the small vessel which had been noted externally, posterior and to the right of the pulmonary artery. The orifice of this vessel was small, measuring 1 cm. in circumference. The aortic valve consisted of three normally formed, but minute, cusps. The coronary ostia and distribution of the coronary arteries were normal. The circumference of the ascending aorta measured 1.1 cm. The brachiocephalic vessels were given off normally. The circumference of the transverse aorta measured 1 cm., whereas that of the descending aorta measured 1.2 cm.

Histologic study of the myocardium revealed a moderate increase in connective tissue in the right ventricular septal myocardium adjacent to the endocardium. The vessels showed no changes. The fibers of the myocardium of the right ventricle were distinctly larger than those of the left ventricle. The mitral and tricuspid valves showed no changes.

The Purkinje system was studied by incomplete serial sections, stained with hematoxylin and eosin and by the van Gieson method. The auriculoventricular node and the bundle of His and its two arborizations were clearly recognizable anatomically. There was no pathologic change in the auriculoventricular node

(Fig. 11). However, in the center of the bundle of His there was an oval mass of connective tissue which displaced the medial fibers of the bundle and sent fibrous cords among the muscle fibers themselves (Fig. 12). Both the right and left bundle branches showed focal degeneration of the fibers and interruptions by connective tissue (Figs. 13 and 14).

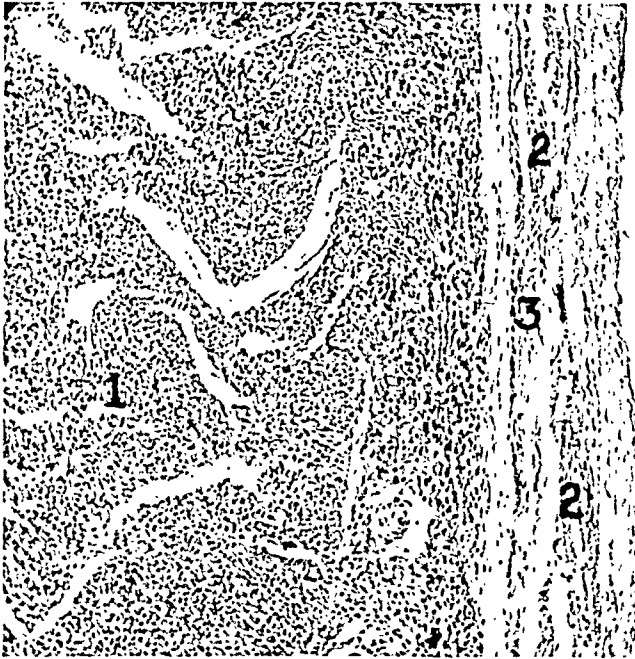


Fig. 13.—Left bundle branch in Case 2. Hematoxylin-eosin preparation, $\times 72$. Connective tissue in the endocardium interrupts the continuity of the muscle fibers; 1, ventricular musculature; 2, bundle branch; 3, connective tissue interruption.

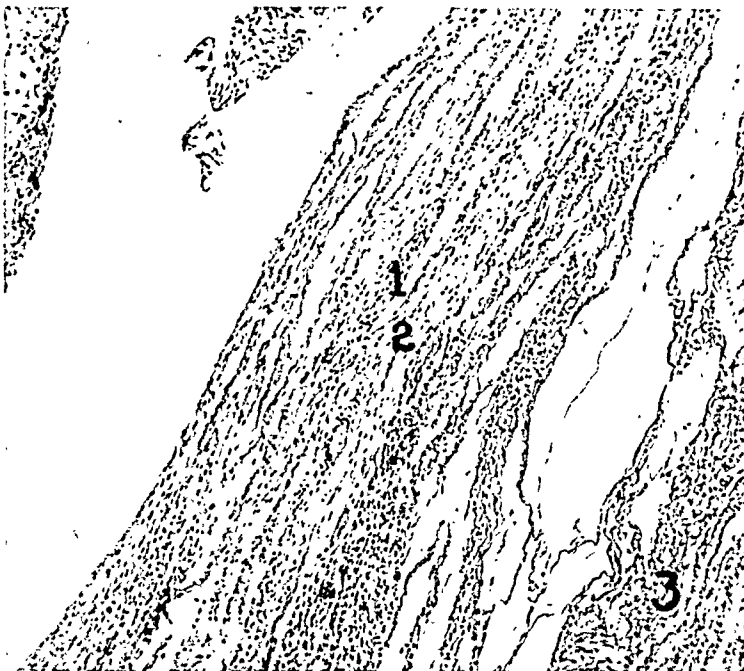


Fig. 14.—Right bundle branch in Case 2. Hematoxylin-eosin preparation, $\times 64$. Note the marked replacement of the muscle fibers of the bundle by endocardial connective tissue; 1, bundle branch fibers; 2, connective tissue; 3, ventricular musculature.

ANATOMIC AND EMBRYOLOGIC DISCUSSION

The anatomic features common to both hearts were: (1) hypoplasia of the ascending and transverse portions of the aorta; (2) hypoplasia of the left auricle, ventricle, and mitral orifice; (3) patent ductus arteriosus and foramen ovale; (4) complete ventricular septum; (5) marked hypertrophy and dilatation of the right auricle and ventricle; (6) no transposition; and (7) abnormal Eustachian and Thebesian valves. In addition, there were, in the first case, (1) atresia of the aortic orifice; (2) marked fibrous thickening of the endocardium of the left ventricle; (3) diffuse equal thickening of the mitral leaflets; and (4) an incompletely divided tricuspid pulmonic valve, and in the second case, (1) hypoplasia of the aortic orifice, and (2) bicuspid "tricuspid" valve.

Case 1 thus belongs to type 2 (a) of our classification, and Case 2 belongs to type 2 (b). In type 2 there is no transposition of the arterial trunks, a defect of the auricular septum is always present, and there may be a defect of the ventricular septum. The ductus arteriosus is usually patent, and there are hypertrophy of the right ventricle and a varying degree of hypoplasia of the left ventricle. When there is aortic atresia or stenosis, with or without mitral atresia or stenosis, the left ventricle is minute or absent, and its endocardial lining usually presents marked fibrous thickening. There may be various minor associated lesions, such as an abnormality of the valves, including the Eustachian and Thebesian valves.

In type 1, hypoplasia of the aorta is associated with various types of transposition of the arterial trunks. Although it is usually the pulmonary trunk which is inhibited in transposition (tetralogy of Fallot), occasionally the reverse may be true (tetralogy of Eisenmenger¹²).

There are various degrees of hypoplasia of the aorta. In some cases both the ascending and transverse portions are involved to a similar degree. In others, accompanying a hypoplasia of the ascending portion, which gives off the brachiocephalic vessels, there is absence of the isthmus (coarctation of the fetal type). In these instances, the pulmonary artery leads through the ductus into the descending aorta. In others, the ascending aorta is converted into a small, thin-walled vessel which ends blindly at the base of the heart, where the coronary arteries are given off. The aortic orifice may be atretic, stenotic, or hypoplastic.

When the aortic trunk is converted into a minute vessel which does not empty into the heart, the anomaly has been called *truncus solitarius pulmonalis*, as differentiated from *truncus arteriosus communis* persists and *truncus solitarius aorticus*. Although the latter two are usually associated with transposition, *truncus solitarius pulmonalis* may or may not be associated with transposition.

The embryologic variant in hypoplasia of the aorta without transposition is some abnormality in the primitive aortic arch system. The normal definitive aorta is derived from the ventral half of the truncus,

a small part of the fourth right aortic arch, all of the fourth left aortic arch, and the common dorsal aorta. In view of the fact that the aorta in these cases is usually normal distal to the entry of the ductus arteriosus, the anomaly is not to be looked for in the primitive common dorsal aorta. The anomaly likewise does not lie in the fourth right arch, for this would separate the brachiocephalic vessels from the ascending aorta—a condition which does not occur with this anomaly. Therefore, the following possibilities remain: (1) hypoplasia of the fourth left arch, or (2) primary abnormal spur formation between left arches four and six, leading to an abnormal aorticopulmonary septum and uneven division of the truncus. In view of the frequent absence of the isthmus with this anomaly, the first explanation is more likely. Hypoplasia of the aorta is best explained as a result of hypoplasia of the fourth left arch, resulting in unequal division of the truncus. When the anomaly is accompanied by transposition, there is, in addition, an abnormality in the absorption of the bulbus.¹³

STUDY OF THE CONDUCTION SYSTEM

Histologic study of the conduction system in both hearts revealed an increase in connective tissue in the region of the bundle of His and focal degenerative changes in the branches (the right was not found in the first case), with a focal increase in connective tissue. We are unable to say whether this increase in connective tissue in the region of the main bundle constituted an abnormality in formation or was the result of inflammatory changes. It was most likely related to the abnormal formation of the base of the aorta.

The pathologic changes may be correlated with the electrocardiograms. Both infants showed first degree auriculoventricular block (prolonged P-R interval). In Case 1, the P-R interval was 0.16 second; in Case 2, the P-R was 0.20 second. In the newborn the normal P-R duration is between 0.08 and 0.13 second.¹⁴ The prolongation of the P-R interval was probably caused by damage to the bundle of His.

Both infants had intraventricular block. Prolongation of QRS is rare in cases of congenital heart disease.¹⁵ In fact, Schnitker,¹⁶ in his review of the literature, was able to find only ten cases. The QRS duration in our first case was 0.14 second; in the second, it was 0.08 second. The normal QRS duration in the newborn is between 0.04 and 0.06 second.¹⁴ The prolongation can be accounted for by the abnormalities in the conduction system in each case, namely, increased connective tissue in the region of the bundle of His and focal degeneration and increased connective tissue in the bundle branches.

Such correlations of electrocardiographic and histopathologic studies of the conduction system are of importance in evaluating the role of the specialized muscular system in the conduction of the cardiac impulse. The recent work of Glomset and Glomset¹⁷ and the older work of Todd¹⁸ have questioned the role of the Purkinje system as a conducting system.

In our cases there were sufficient anatomic changes in the conduction system to account for the heart block which was present.

CONCLUSION

Two cases of aortic hypoplasia without transposition are presented, together with electrocardiographic and histopathologic studies. In these cases there was anatomic evidence of interruptions in the conduction system, and this probably accounted for the heart block which was present.

We wish to express our appreciation to Dr. Louis N. Katz, of the Cardiovascular Department, and Dr. Otto Saphir, of the Pathology Department, for their valuable suggestions.

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FIVE-YEAR SURVIVAL AFTER PERFORATION OF INTERVEN-
TRICULAR SEPTUM CAUSED BY CORONARY OCCLUSION:
HISTOLOGIC STUDY OF KIDNEYS AFTER 350
INJECTIONS OF MERCURIAL
DIURETICS

FRANCIS C. WOOD, M.D.,* AND MARY MILLER LIVEZEY, M.D.
PHILADELPHIA, PA.

THIS report is published for the following reasons: (1) The patient lived almost five years after acquiring a ventricular septal perforation through an area of infarction. (2) During this interval he received 350 injections, totaling about 650 c.c., of various mercurial diuretics, and, at necropsy, there was no histologic evidence of renal damage.

CASE REPORT

C. W. H., a white man, 44 years of age, was referred to us October 16, 1936, by Dr. Isaac Starr, who had just seen him for the first time. In 1935 he began to notice constriction in the middle of his chest and aching in both clavicular regions on strenuous exertion; these symptoms were relieved by rest. On September 15, 1936, after running 200 yards in a rainstorm, he had an attack of severe pain in the sternal region, epigastrium, throat, and left arm, associated with inability to get his breath. The pain persisted through the day, even at rest, and was relieved only by a hypodermic. He remained in bed thirty-six hours, and then went about his business as a real estate agent. On September 17 he had another attack of pain which lasted several hours, but from that time until we first saw him, almost a month later, he complained chiefly of dyspnea on exertion, with only occasional pain in the chest.

Examination showed a somewhat pallid, thin man, with a heart rate of 130 per minute and a blood pressure of 165/110. Systolic murmurs were heard at the apex and aortic area. There were no signs of congestive heart failure.

The erythrocyte count was 4,000,000, the hemoglobin, 75 per cent, and the leucocyte count, 12,000. The blood sedimentation rate (Cutler) was 26 mm. in one hour. The cardiac silhouette area was 30 per cent above the predicted figure (orthodiagram). The electrocardiogram showed evidences of former infarction in the posterior wall of the left ventricle (Fig. 1A). A diagnosis of unhealed cardiac infarction was made and the patient was sent home to bed.

On October 23, 1936, one of us (F. C. W.) saw him at his home, and at that time first noted a loud, rough, systolic murmur and thrill over the lower sternal region. The blood pressure on that day was 145/105. The blood sedimentation rate was 21 mm. in one hour (Cutler). A diagnosis of perforation through an infarcted area in the ventricular septum was made.

On November 6, 1936, hepatic and venous engorgement was noted for the first time. The blood pressure was 125/90; the pulse rate was 120 per minute; and the

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

Received for publication May 18, 1942.

*Major, Medical Corps, U. S. Army, Twentieth General Hospital.

blood sedimentation rate (Cutler) was 18 mm. in one hour. On November 13, 1936, he began to have some choking at night which was relieved by sitting up; the veins and liver were more engorged. On November 23, 1936, edema of the feet was first observed. He grew steadily worse until, on December 27, 1936, he was admitted to the Hospital of the University of Pennsylvania with severe congestive heart failure. He then volunteered the information that, instead of remaining in bed at home, as we thought he had done, he had begun to work shortly after we first saw him, making as many as forty calls a day. We were unable to obtain any history to suggest exactly when his septal perforation had occurred.

At the time of this admission to the hospital, he had cyanosis, dyspnea, Cheyne-Stokes respiration, orthopnea, edema up to the costal margins, marked engorgement of the veins and liver, and ascites. He suffered recurring attacks of severe anginal pain, especially after eating. He was mildly psychotic, particularly on awaking from sleep. The blood pressure averaged 150/115, the pulse rate, 95, and the respiratory rate, 24. The erythrocyte count was 4.4 million, the hemoglobin, 81 per cent, and the leucocyte count, 8,700, with a normal differential count. The blood Wassermann reaction was negative. The urine showed a specific gravity of 1.028, an acid reaction, a trace of albumin, many hyaline casts, a few leucocytes, and no erythrocytes. The electrocardiogram was the same as before. Treatment consisted of rest, opiates, barbiturates, nitroglycerine, xanthines, ammonium nitrate, salyrgan, and digitalis. At first the output of urine was small. After a week, slow improvement began. The urine output became adequate, and the blood pressure dropped to 125/75. He went home January 16, 1937, and gradually gained strength.

For the rest of his life his legs were edematous. The edema was treated with salyrgan and méreupurin intravenously, usually the former because he preferred it. He received six to eight injections a month, at first 1 c.c. but after May 27, 1937, 2 c.c. His total dose was not accurately recorded, but from the time of his first injection, on December 30, 1936, until the time of his last, on August 18, 1941, he must have received about 350 injections and a total dose of about 650 c.c., all in the same large right antecubital vein, without extravasation or thrombosis. On one occasion he was given a mercurin suppository, but intense rectal irritation ensued, and the intravenous route was used thereafter. The diuresis produced by these drugs was quite satisfactory on almost all occasions; a loss of weight of about five pounds occurred each time. The diuresis was sometimes increased by ammonium nitrate administration and by salt restriction. However, the benefit derived from these two additional measures did not seem to the patient to be sufficient to warrant the trouble and discomfort involved in their use. Restriction of fluid intake did not seem to help much, so he abandoned it. Digitalis was given from time to time, but we saw no evidence of benefit from it, and the patient thought it made him feel worse. When he had unusually good diuresis (every second or third time he received an injection) he experienced a symptom which we had not encountered previously in any other patient. The drug was usually given about 3:00 p.m. The next morning, on arising, he experienced severe pain in the legs, located along the front of the lower leg and especially just external to the tibia. It was more marked in the left leg, which was the more edematous of the two. It lasted fifteen to twenty minutes, and was very intense. He said it felt as if someone had taken his foot and bent it forward and up to touch his knee.

Despite the long continued use of mercurial diuretics the patient never showed obvious clinical evidence of renal damage. The urine throughout showed a trace of albumin and sometimes a number of hyaline casts, but nothing more than would be expected in any cardiac patient with this degree of venous engorgement. There were a few leucocytes but no erythrocytes.

During the summer of 1937, the ascites, which had been present since December, 1936, disappeared and never returned in recognizable amount. On August 10, 1937,

he experienced recurring pain in the right side of the chest and developed pleural effusion on that side. He was readmitted to the hospital August 19. The right side of the chest was tapped, and a liter of sterile, bloody fluid was obtained. With the onset of pleural effusion he developed trepopnea.¹ During this hospital admission the electrocardiogram showed nothing new, the blood sedimentation rate was 3 mm. in one hour (Cutler), and the blood cell count was essentially the same as on the previous admission. The urine was negative except for a trace of albumin. The blood urea nitrogen was 22 mg. per cent, and later fell to 16 mg. per cent. The blood sugar was 75 mg. per cent. The serum proteins were 6.7 per cent. He left the hospital August 21, 1937, but during the next sixteen months returned periodically for thoracentesis. The character of the fluid was that of an exudate, rather than a transudate. On November 7, 1937, after tapping, a pleural friction rub was heard. As time went on the fluid became less bloody, and finally became clear. On December 23, 1938, the last (sixty-first) thoracentesis was done. After that the fluid ceased to accumulate and his condition remained more or less stationary.

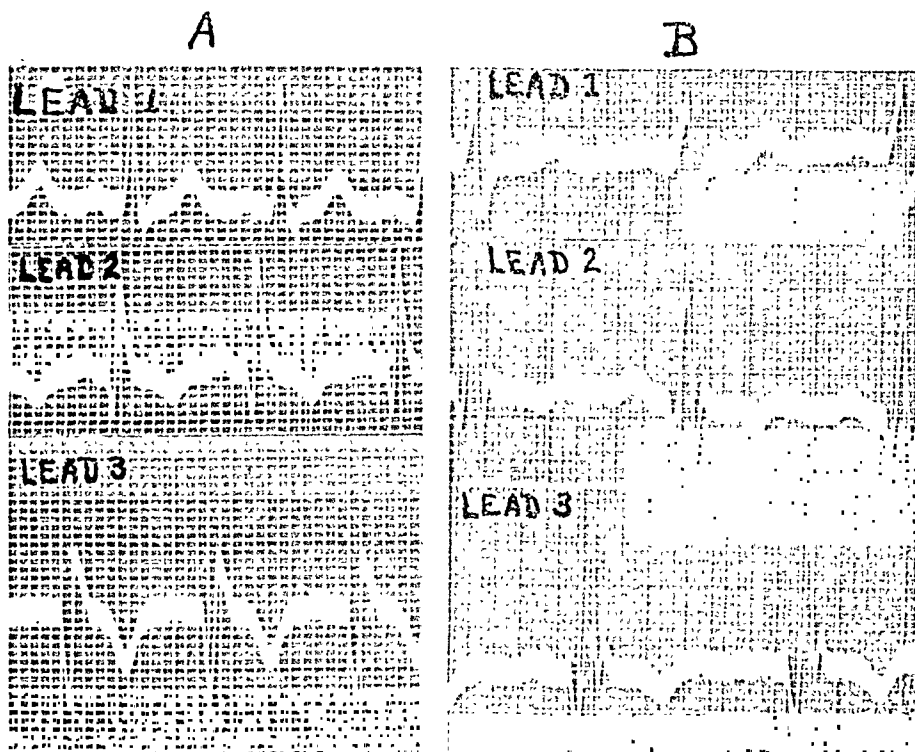


Fig. 1.—A. Electrocardiogram taken October 16, 1936. The QRS complexes are slurred and their duration is 0.10 second. Q waves and inverted T waves in Leads II and III indicate infarction involving the posterior wall of the left ventricle. The RS-T segment shows no deviation from the isoelectric line, but the clinical observations suggested active infarction.

B. Tracing taken August 18, 1941. The duration of the QRS complexes is 0.12 second, and a conduction defect of the right bundle branch type is present. Q_2 and Q_3 and inversion of T_2 and T_3 are still present.

The electrocardiogram throughout the last four years of his life showed signs of a healed posterior infarction, and some widening of the QRS complex suggesting a right bundle branch conduction defect (Fig. 1B). The heart increased in size slowly from an area of 146 sq. cm. on October 16, 1936, to 189 sq. cm. on August 18, 1941, (orthodiagram of the posteroanterior silhouette). The blood sedimentation rate remained very slow, never exceeding 3 mm. in one hour (Cutler) after the original infarct had healed.

Despite the fact that he always looked like a person in the terminal stages of cardiac failure, and despite our attempts to induce him to take adequate care of himself, he continued his occupation as a real estate agent. He worked an average of eight hours a day, traveling about the city and climbing stairs. Now and then he would indulge in unusual effort, such as chopping wood or running to avoid getting wet in the rain, which sometimes precipitated cardiac pain, intense dyspnea, dizziness, and a throbbing pain in the region of the liver. Each attack of this sort looked as if it might be his last. However, in a few days he would regain his ordinary level of chronic ill health.

During the night of August 28, 1941, he developed pain in the anterior, middle portion of the chest, which disappeared and reappeared periodically. On the evening of August 30, 1941, he had an unusually severe attack. The blood pressure dropped from its former level of 150/110 to 125/70. He was readmitted to the Medical Ward of the Hospital of the University of Pennsylvania on the service of Dr. O. H. P. Pepper at 10:00 P.M. on August 31, 1941. The blood pressure fell to 75/65, he became more cyanotic, gradually lost consciousness, and died. The clinical impression was that his death was caused by coronary insufficiency and myocardial ischemia.

The necropsy was performed by Dr. Warner F. Sheldon, twelve hours after the patient's death.

The legs were edematous; the skin of the lower part of the legs showed a brownish mottling, and appeared thin and somewhat atrophic. No intra- or extra-pericardial adhesions were found. The heart weighed 840 grams. All of the valves were smooth, thin, and intact, except for small fibrous thickenings of the mitral valve leaflets. The right ventricle was markedly dilated and its walls were hypertrophied, measuring 1.0 cm. in thickness. The left ventricular wall measured 1.5 to 1.7 cm. in thickness. The left ventricular cavity showed dilatation, but proportionally less than the right ventricle. The right coronary artery was completely blocked by a firm nodule about 7 cm. from its origin, for a distance of 0.6 cm. Beyond this, the vessel was patent but small. There was an area of old infarction in the posterior, upper part of the septum and in the adjacent posterior wall of the heart. A fairly large perforation, 1.5 cm. in diameter, was found in the infarcted area of the ventricular septum. The opening into the left ventricle was easy to see; that into the right ventricle was more difficult to find because it was hidden behind a papillary muscle (See Fig. 2, *A* and *B*). The margins of the septal perforation were smooth and grayish, surrounded by fibrous tissue, and covered by endocardium. Obviously the communication was one of long standing. On the inner surface of the right ventricle, where the blood current must have struck the wall after passing through the septal perforation, there were several large, yellowish-gray, elevated plaques, each 1 × 2 cm. In the posterior, upper, left ventricular wall, adjoining the ventricular septum, there was an aneurysmal bulge 4 cm. in diameter; its outer wall was 1 mm. in thickness.

There were no other coronary occlusions and no fresh thromboses were found. The left anterior descending coronary artery was small, and some of its branches showed a few yellow plaques. The left circumflex artery was small, and its walls were smooth and thin.

The lungs showed passive congestion. One healed tuberculous nodule was found in the right upper lobe. There was evidence of former pleurisy on the right side. The pulmonary arteries were prominent, definitely dilated, and their walls were thickened by yellowish-gray, atheromatous plaques. The bronchi were moist and red and contained a little mucoid material.

The liver weighed 1,960 grams. It was pale, grayish brown, and rather firm. The capsular surface was irregular but not nodular. It cut with difficulty, and surfaces made by cutting were pale and yellowish-brown and showed indistinct lobular markings. The hepatic veins were much larger and more prominent than normal. The gall bladder and bile ducts were normal.

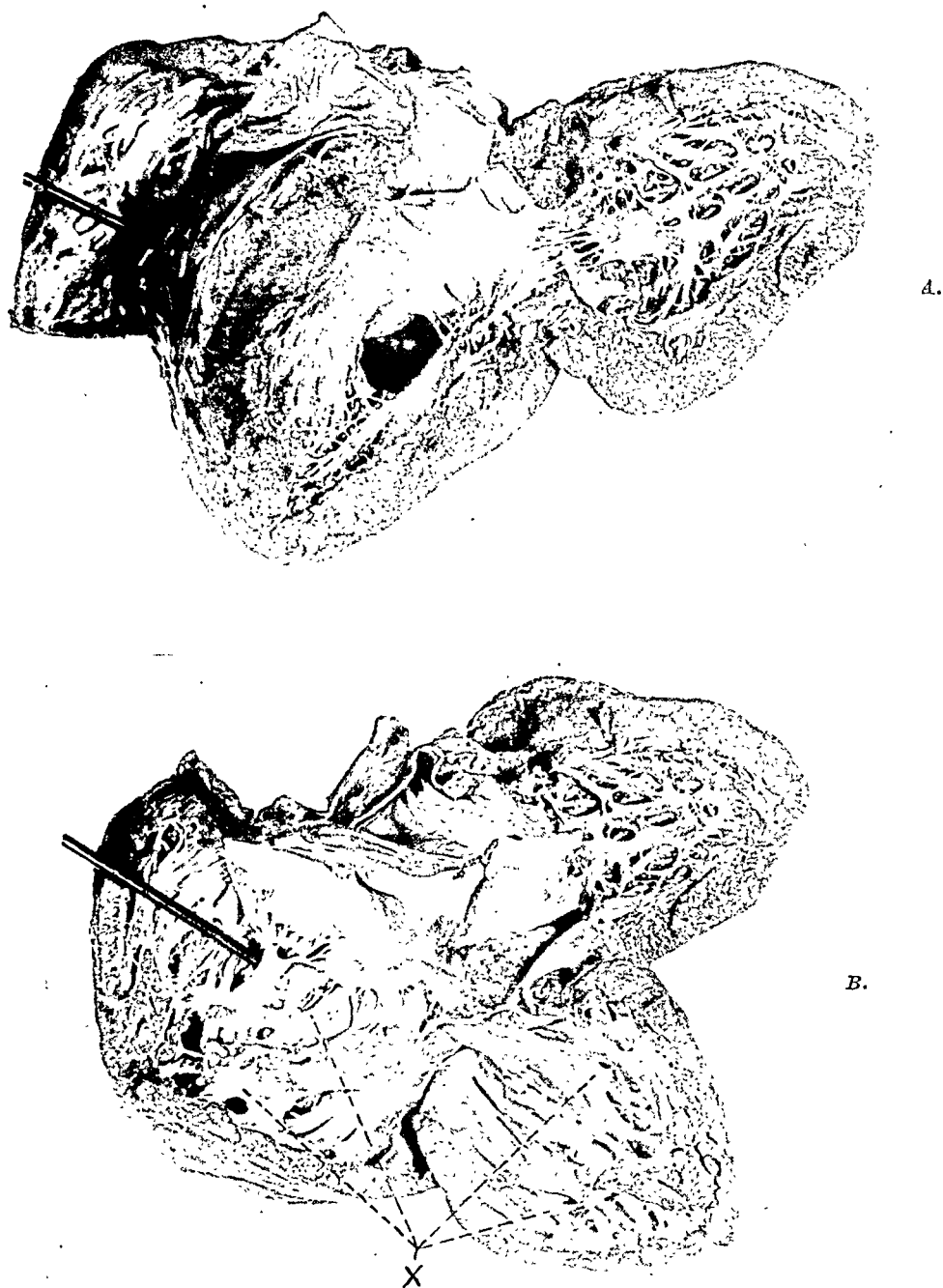


Fig. 2.—A. Heart of C. W. H., with left ventricular cavity exposed to view. The aortic valve is seen above, the mitral valve lies below it. Beneath the mitral valve there is a dark area, roughly 1 x 2 cm. This is an opening into the aneurysm of the posterior wall of the left ventricle, which lies behind the papillary muscle and is formed in part by the ventricular septum. The probe passes through the septal perforation, which enters the aneurysm, and its tip is visible as a shiny spot in the center of the dark area. Note the thickening of the left ventricular wall.

B. The right ventricular cavity opened, with a probe inserted behind a papillary muscle into the opening of the septal defect. "X" indicates the plaques observed where the blood current flowing through the septal defect probably struck the endocardium of the right ventricle.

The kidneys were of normal size, shape, and consistency. The left weighed 160 grams; the right, 140 grams. The capsule stripped with ease, revealing an evenly granular, dark blue surface. The cut surface was dark bluish red and bloody. The cortex was dark blue and the differentiation poor. The pelves, ureters, and bladder were normal.

Many of the organs showed chronic passive congestion, but in other respects were not remarkable.

Histologic Studies.—The larger arteries in the kidneys showed fibrous intimal thickening. The afferent vessels and the remainder of the kidney tissue were normal. Dr. Balduin Lucke, after making a careful examination of the renal tissue, stated that he saw no histologic evidence that the long continued administration of mercurial diuretics had caused kidney damage in this patient (Fig. 3). The liver was the seat of early portal cirrhosis. The lungs showed numerous clumps of phagocytic, brownish, pigmented cells in the alveoli, and some recent hemorrhages. The arterial walls were considerably thickened, both by intimal fibrous plaques and muscular hypertrophy. This arterial change varied considerably from vessel to vessel. The diaphragmatic pleura on the right side showed dense fibrous scarring, with numerous dilated vessels.

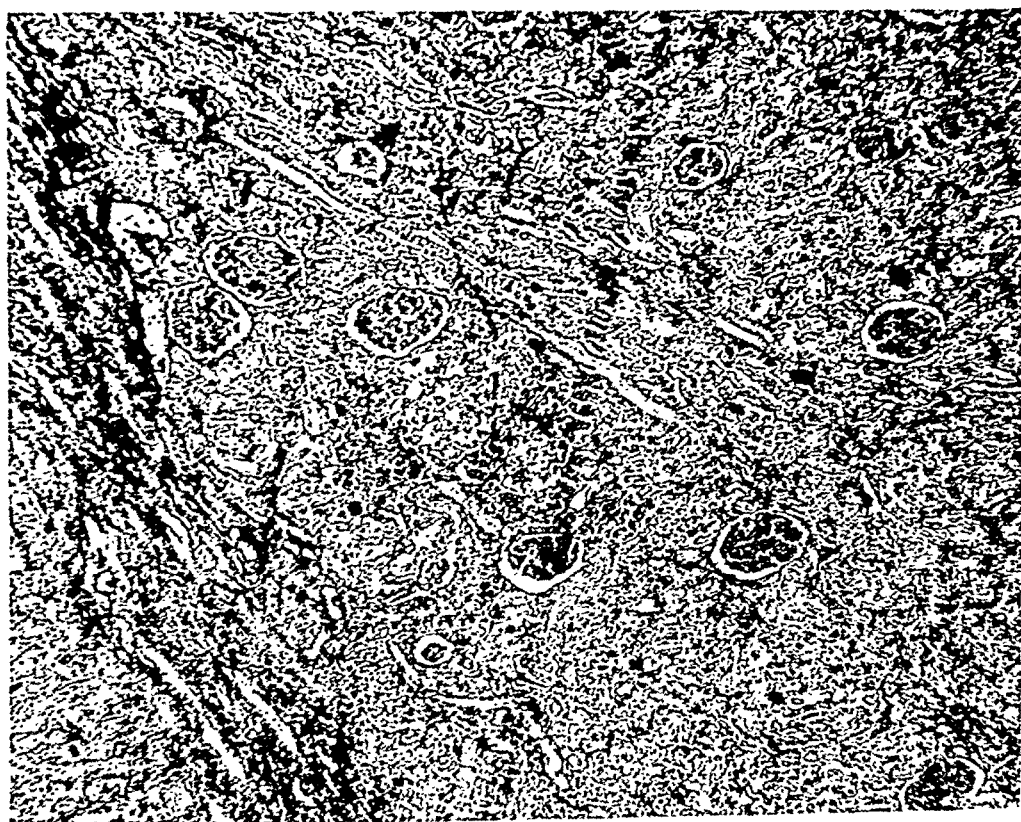


Fig. 3.—Photomicrograph of section of kidney (X37) of C. W. H. No histologic evidence of renal damage was found, despite the prolonged administration of mercurial diuretics.

Heart.—A section from the septum at the edge of the aneurysm showed complete destruction of the muscle and replacement by a narrow band of dense hyaline scar tissue. A little further from the perforation the septum showed large patches of scar tissue between hypertrophied muscle fibers. The scar contained numerous, dilated capillaries. A section from the apex of the left ventricle showed only scattered, small scars. A section from the right ventricle, made through one of the thickened endocardial plaques, showed that these structures were dense, relatively

acellular, hyaline and faintly fibrillar, collagenous scar tissue, confined to the endocardial surface, not extending into the muscle. They were apparently produced by the abnormal blood current striking the endocardium, and were obviously not overlying any areas of myocardial infarction.

In conclusion, the autopsy observations were in keeping with the clinical opinion that the infarct and perforation of the posterior part of the septum occurred at or about the time of the attack in the autumn of 1936, four years and ten months before the patient's death.

DISCUSSION

We have found references to thirty-six cases of interventricular septal perforation through an area of infarction.²⁻¹⁹ Since Sager's² excellent review, a greater number of reports have appeared, and in more cases the diagnosis is being made ante mortem. In seven cases, so far as we know, the condition was diagnosed during the patient's life.^{5, 12, 13, 15-17, 19} As a rule, the diagnosis is relatively easy to make. When a patient with a recent cardiac infarction develops a loud, rough, systolic murmur and thrill in the lower sternal region, which had not been present before, the chance that an acquired septal perforation has occurred is great. Usually there is an attack, or some abrupt change for the worse in the patient's condition, to signal the moment of the perforation, although we could not ascertain the exact time in our case. There are only three possible difficulties, of which we are aware, in making the diagnosis: (1) A patient with a congenital interventricular septal defect, who subsequently developed a cardiac infarct, if not seen prior to the infarction, might be thought to have acquired the septal perforation through an infarcted area. (2) Rupture of a papillary muscle after cardiac infarction might conceivably produce a murmur which could be confused with that of an acquired septal perforation (Brunn,¹⁶ Case I). We have never seen an example of this lesion, but Voigt²⁰ has published a complete review of all the nine known cases. Eight of these were probably the result of cardiac infarction. In four of the nine cases reported by Voigt there were no striking auscultatory abnormalities. (3) In certain patients with coronary thrombosis and septal perforation and with marked depression of the circulation, the murmur may be absent (Bickel and Mozer,³ Case 2) or not very loud, and the thrill may be absent.

The location of the recent infarct in the majority of the reported cases was in the anterior surface of the left ventricle. The subject of this case report is one of the few with posterior infarction. We know of only five others in which septal perforation occurred as a result of posterior infarction.^{3, 10, 13, 16, 18}

The duration of life in these cases is usually very short after the septal perforation takes place. Only seven of the reported patients are thought to have lived more than a month,^{6, 9, 11, 12, 15, 17, 19} and none of these is known definitely to have lived as long as a year. Therefore, our patient, who lived four years and ten months after the development of signs of septal perforation, survived at least four years longer than any other

patient of whom we are aware. He was a relatively young man who had an occlusion of the right coronary artery, but, subsequent to the original attack, he had no further coronary thrombosis. The fact that a fairly small part of his myocardium was damaged may account for his long survival.

Stern's¹⁰ patient was the only other one to whom we could find reference in the literature with a right bundle branch conduction defect. This may have been caused by damage to the right branch of the bundle of His as a result of the infarction and septal perforation.

All patients who have survived an acquired septal perforation for any length of time have shown "right ventricular" failure, of which the outstanding features are cyanosis, edema, hepatic and venous engorgement, and often ascites.

There are a number of reports in the literature of long continued administration of mercurial diuretics without clinical evidence of renal damage.²¹⁻²⁸ The reports with necropsy study of the kidneys are relatively few, and the amounts of diuretic received are relatively less (240 c.c., maximum).^{29, 30} We have not made a complete survey of the literature, but we have not encountered a report of any patient who received as much as our patient did and who subsequently came to necropsy.* He had about 350 injections, and a total amount of about 650 c.c., over a period of four and a half years, and, at necropsy, showed no evidence of renal damage.

SUMMARY

The patient described in this report had coronary occlusion in 1936, at the age of forty-four, and perforation of the ventricular septum through the infarcted area; he lived four years and ten months after this complication occurred. He led a fairly active existence during that time, despite continued congestive heart failure. He received approximately 650 c.c. of mercurial diuretics to control edema. No evidence of renal damage was found at necropsy.

We wish to express our appreciation to Dr. Balduin Lucke and to Dr. Warner F. Sheldon for making the pathologic studies described in this report.

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THE EFFECTS OF POSTURE ON THE VELOCITY OF BLOOD FLOW FROM ARM TO TONGUE

MORRIS WILBURNE, M.D.
CHICAGO, ILL.

A MARKED divergence of opinion exists as to the effects of posture on the velocity of blood flow and on cardiac output. Thompson Alper, and Thompson,¹ employing brilliant vital red, observed a pronounced increase in both the arm-to-foot and foot-to-arm circulation times in the standing-still posture, as compared to the recumbent position. Further, when they produced moderate venous congestion in a lower extremity by the application of a tourniquet, with the subject in the recumbent position, the appearance of the dye was delayed to approximately the same degree as in the standing-still position. Bock, Dill, and Edwards² found that the histamine circulation time (ankle-to-face) in the standing position was $1\frac{1}{2}$ to $4\frac{1}{2}$ times greater than in the recumbent position. Mayerson, Sweeney, and Toth,³ who studied eleven normal male subjects, observed a marked increase in circulation time when the subject was tilted passively from the horizontal position to an angle of 75° with the horizontal; the testing agent⁴ was injected into the foot vein. However, in those instances in which the agent was injected into the antecubital vein, their results were equivocal. Kvale and Allen⁵ noted a longer arm-to-foot circulation time⁴ in the upright posture than in the recumbent position, but the arm-to-tongue results were variable, i.e., the time was increased in 4 subjects, reduced in three, and unchanged in one. More recently, Main and Baker⁶ found no significant difference in arm-to-tongue circulation time (calcium gluconate) between the recumbent and standing positions in eleven subjects.

In accord with the observation that there is a reduction in velocity of blood flow in the upright posture, many investigators⁷⁻¹³ have found that the minute cardiac output is reduced in the upright posture. Conversely, the contention of some workers^{14, 15, 16} that posture exerts no influence on cardiac output would tend to support those studies in which blood velocity was found to be unaffected by changes in posture.

The present study was undertaken to compare the arm-to-tongue time in two positions, namely, with the body horizontal, and with the legs dependent.

METHOD

Twenty-one male and three female subjects between the ages of 20 and 72 years were studied. All but one were either free of heart disease or exhibited no clinical evidence of congestive heart failure; the exception had slight signs of congestion.

From the Cardiovascular Department, Michael Reese Hospital, Chicago, Ill.
Aided by the A. D. Nast Fund for Cardiovascular Research, and the John D. and Fanny K. Herz Fund.

Received for publication May 6, 1942.

Each subject rested 10 to 15 minutes in the recumbent (horizontal) position. The circulation time from an antecubital vein to the tongue was then measured with calcium gluconate,* using 4 c.c. of solution. The subject was then propped up in a comfortable sitting position, with both legs dependent over the edge of the bed; care was taken that muscular effort be avoided or kept at a minimum during the change of position. After another 10 to 15 minutes' rest, the circulation time was again measured. The patient was then returned to the previous recumbent position, and, after another rest of 10 to 15 minutes, a third measurement was made. All injections were made into the antecubital vein at the level of the right auricle. A total of 73 measurements was taken; a fourth test was made in one case as a check (40 minutes after the third measurement) because of a series of unexpectedly high figures.

RESULTS

The circulation time was greater in the sitting, legs-dependent position than in the recumbent position in 15 subjects, less in 7, and equivocal in 2. Of the 15 subjects who had a longer circulation time in the sitting, legs-dependent position, 12 showed an average recumbent circulation time within the normal limits of 8 to 16 seconds, and 3 exceeded 16 seconds. Of the 7 subjects whose circulation time was less in the sitting, legs-dependent position, 5 had an average recumbent time greater than 16 seconds (2 of these were subjects with auricular fibrillation without demonstrable congestion), and 2 exhibited a normal recumbent time. In the 2 instances in which the results were indefinite, the average recumbent time was normal.

DISCUSSION

Some of the slight changes in circulation time between the recumbent and the sitting, legs-dependent position were probably within the limits of experimental error. However, in many cases the figures were sufficiently different to indicate changes outside the experimental error, especially since the effect was reversible. Even the slight changes in circulation time in some of our patients were probably real because they were also reversible, but the fact that the differences sometimes approached the experimental error makes the results less striking and may explain some of the differences between our results and those previously reported. The contradictory observations in some previous reports may also have been the result of failure in some cases to consider the fact that in the standing position there are increased muscular tone and swaying which exert a milking action on the venous reservoirs, so that there is less pooling than occurs in the sitting, legs-dependent position.

However, some of the differences are the resultant of two opposite effects of the change in posture on circulation time, namely, (a) a reduction in the venous return in the sitting, legs-dependent posture, and (b) a narrowing of the vascular bed between the point of injection and

*A 20 per cent solution of calcium gluconogalactogluconate (Neo-Calglucon) was generously supplied by the Sandoz Chemical Works.

TABLE I

SUBJECTS WITH INCREASED CIRCULATION TIME IN SITTING, LEGS-DEPENDENT POSITION

<i>I. Subjects With Normal Average Recumbent Time</i>						
NO.	SUBJECT	AGE YEARS	DIAGNOSIS	RECUMBENT SEC.	SITTING, LEGS-DEPENDENT SEC.	RECUMBENT SEC.
1.	E. A.	36	Diabetes mellitus	12.7	16.4	12.2
2.	C. C.	38	Cholecystitis	12.8	16.5	14.7
3.	S. S.	42	Diagnosis undetermined (No cardiac disease)	15.3	20.0	16.2
4.	E. L.	35	Diagnosis undetermined (No cardiac disease)	12.7	17.4	12.8
5.	R. J.	45	Hemorrhoids; hernia	14.3	15.4	12.2
6.	J. N.	44	Old (3 years) healed myocardial infarct	11.0	13.2	12.0
7.	A. V.	33	Anorexia and weakness of undetermined etiology (No cardiac disease)	10.8	11.9	10.4
8.	E. V.	35	Amebiasis	10.3	11.3	9.7
9.	J. S.	41	Pneumonia (recovered)	10.8	12.4	11.7
10.	F. K.	37	Epilepsy	13.4	14.7	13.9
11.	M. S.	20	Chronic ulcerative colitis	11.0	11.7	10.3
12.	S. B.	66	Anal fistula	13.5	15.2	15.0
<i>II. Subjects With Prolonged Average Recumbent Time</i>						
1.	I. K.	54	Beriberi heart disease (treated)	16.0	17.0	16.2
2.	P. H.	45	Pneumonia (recovered)	18.0	19.6	16.0
3.	L. R.	48	Arteriosclerotic heart disease	20.0	23.8	15.1
			Diabetes mellitus			
			Early signs of congestive failure			

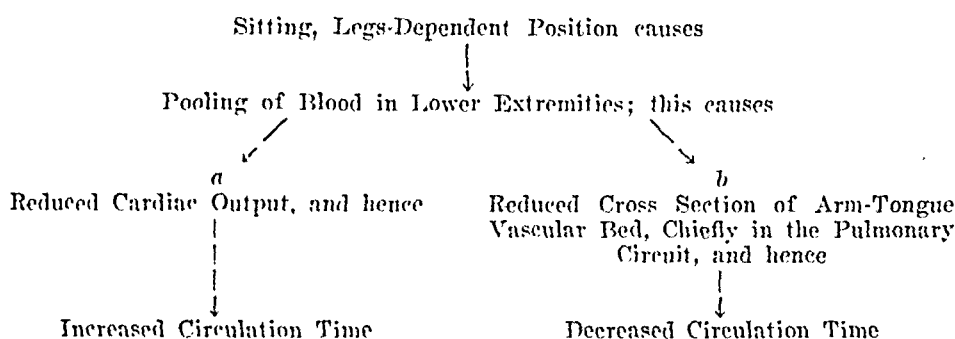
TABLE II

SUBJECTS WITH DECREASED CIRCULATION TIME IN SITTING, LEGS-DEPENDENT POSITION

<i>I. Subjects With Normal Average Recumbent Time</i>						
NO.	SUBJECT	AGE YEARS	DIAGNOSIS	RECUMBENT SEC.	SITTING, LEGS-DEPENDENT SEC.	RECUMBENT SEC.
1.	L. S.	33	Hernia	12.4	10.6	11.8
2.	H. C.	50	Rheumatoid arthritis	12.4	10.1	10.7
<i>II. Subjects With Prolonged Average Recumbent Time</i>						
1.	S. B.	72	Arteriosclerotic heart disease, auricular fibrillation. (No clinical evidence of congestion)	26.0	22.4	29.6
2.	L. M.	69	Arteriosclerotic heart disease (Noncongestive)	16.3	13.9	16.4
3.	J. M.	58	Diabetes mellitus	21.4	18.6	25.0
			Angina pectoris (No clinical evidence of congestion)	Recumbent repeated 40 min. later 24.8		
4.	L. B.	53	Neuritis? (No clinical evidence of congestion, or heart disease)	18.4	16.8	17.3
5.	N. M.	52	Auricular fibrillation, etiology undetermined. (No clinical evidence of congestion)	18.0	16.4	17.2

the point of response, especially in the pulmonary bed. It would appear that in health the effect of mechanism *a* (Diagram I) predominates, but not always sufficiently to neutralize the effect of mechanism *b*. In congestive heart failure, whether recognizable or not, with its increase in circulating blood volume, the effect of mechanism *b* appears to predominate usually.

Diagram I



The results of this study offer an objective measure of the diminution of pulmonary engorgement brought about by the supine posture, with legs dependent, in cases of orthopnea. The spontaneous tendency of patients with congestive failure to assume the legs-dependent position at the edge of the bed is probably explained by the fact that this position lessens pooling of blood in the lungs. Our results support the contention that a reduction in minute cardiac output and pulmonary stasis occurs in the upright posture, incident to a diminution in circulating blood volume¹⁷ caused by pooling of blood in the lower extremities.¹⁸ When there is congestion of the lungs, the latter effect dominates; otherwise, the former tends to be the more prominent.

SUMMARY AND CONCLUSIONS

Circulation time studies by the calcium gluconate arm-to-tongue method indicate that when the circulation time in the recumbent position is normal, the values in the sitting, legs-dependent position (which eliminates to a large extent the muscular contractions and swaying incident to standing) tend to be higher than in the recumbent position. However, when the circulation time in the recumbent position is prolonged, the circulation time in the upright position tends to be lower. This substantiates the observations that minute cardiac output is less in the sitting and standing positions than in the recumbent position. However, the decrease in the pulmonary bed on changing from the recumbent to the upright position is apparently relatively greater in patients with congestive heart failure than in normal persons.

I wish to express my appreciation to Dr. L. N. Katz, under whose guidance this study was undertaken, for his valuable advice and criticism.

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THE USE OF PAPAVERINE AS AN OBJECTIVE MEASURE OF CIRCULATION TIME

STEPHEN R. ELEK, M.D., AND SYLVAN D. SOLARZ,* M.D.
CHICAGO, ILL.

DESPITE the development and application of numerous methods for measuring circulation time in man,¹⁻² there are few that are simple, reliable, and objective. In the course of clinical studies of papaverine hydrochloride, a sudden deepening of respiration shortly after injection was almost uniformly noted; this observation suggested that this drug might be used to obtain an objective measure of circulation time. This report presents a discussion of the method evolved and the results obtained in normal and in some abnormal states.

TECHNIQUE

After preliminary tests, the following technique was established. The patient lies supine in a quiet room for at least five minutes before the test is performed. He is informed about what will probably occur and asked to refrain from coughing, sighing, or voluntarily taking a deep breath. The pulse and respiratory rate are noted, and particular attention is paid to the depth and character of the respiration (intercostal and abdominal breathing), so that changes may be quickly observed. The antecubital vein is used for injection, and for this purpose the arm is placed on a pillow so that the level of the site of injection is about 10 cm. above the posterior axillary line. A 2 c.c. Luer syringe and a 20-gauge needle are employed for the injection. About ten seconds are allowed to elapse between insertion of the needle and injection of the drug in order to circumvent the circulatory effects of the prick of the needle and the venous congestion produced by the tourniquet. The papaverine hydrochloride† is injected within one second, and the circulation time is clocked with a stop watch in the usual way. The end point will be described below.

End Point.—The end point is similar to that observed by Robb and Weiss³ with the sodium cyanide method. It is signalled by a sudden, deep inspiration, with employment of the abdominal muscles, which interrupts the usual phase of respiration, and is at times accompanied by a sigh or gentle exclamation. This is commonly followed by visible flushing of the face or cheeks, or a feeling of facial warmth, a sensation of throbbing in the temples, mild dizziness, and, less frequently, acceleration of the heart. The tachypnea lasts fifteen to sixty seconds, averaging about thirty seconds. It is usually not distressing, and the other symptoms are well tolerated when the recommended dose is used. The end point is sharp and easily recognized. In dyspneic patients it is manifested by a sudden, deep inspiration, together with full use of the intercostal muscles, especially the upper ones.

From the Cardiovascular Department, Michael Reese Hospital, Chicago.

Aided by the A. D. Nast Fund for Cardiovascular Research.

Received for publication May 13, 1942.

*Sunset Camp Fellow.

†Kindly supplied by Dr. K. K. Chen, of Eli Lilly and Company.

Dosage.—After extensive preliminary trials we found that 40 mg. (1.25 c.c.) was the most satisfactory dose; it uniformly gives a sharp end point with a minimum of side reactions. A dose of 32 mg. (1.00 c.c.) may be used successfully, but occasionally we have obtained no end point with it or one that is not easy to distinguish.

That the circulation time was not significantly affected by the amounts used was shown by duplicate measurements on two patients with increasing doses of papaverine hydrochloride, viz., 32, 40, 48, and 56 mg. These amounts were injected at two to ten minute intervals. As shown in Table I, the result was not significantly changed with doses between 32 and 56 mg.* With 48 mg. or more the tachypnea becomes distressing, and the patient complains of feeling "knocked-out"; in addition, headache and a general feeling of weakness may ensue.

TABLE I
EFFECT OF INCREASING DOSES OF PAPAVERINE ON THE CIRCULATION TIME

SUBJECT	DOSE OF PAPAVERINE (MG.)	TIME OF END POINT (SEC.)
1. P. H.	32	25.4
	40	27.0
	48	22.6
	56	21.4
2. L. K.	32	24.8
	40	24.2
	48	24.2
	56	21.6

With doses of 40 mg., duplicate tests may be made at two to five minute intervals without untoward symptoms or a change in the circulation time (Table II). Papaverine is not irritating locally and does not cause necrosis.

RESULTS

Fifty patients,† selected at random, were studied. This group included some patients with heart disease, but without any subjective or objective manifestations of heart failure. There were 41 men and 9 women, and their weights varied from 100 to 200 pounds. The distribution according to age was as follows: 8 were between 15 and 20, 5 between 20 and 30, 9 between 30 and 40, 10 between 40 and 50, 10 between 50 and 60, and 8 between 60 and 70 years of age.

The range of values for the circulation time with papaverine varied from 15.4 to 27.0 seconds; the average was 20.8 seconds.

In 24 of these patients duplicate measurements were done at 2 to 5 minute intervals (Table II). As shown in this table, the reproducibility of the results was good; the range of differences between any two measurements was 0 to 3.0 seconds, and the average, 1.2 seconds.

Table III and Table IV list the data on 6 patients with congestive heart failure and 4 patients with clinical and laboratory evidence of hyperthyroidism, respectively. Measurements with decholin were also made on the former at the same time. In patients with heart failure

*The difference in results with these two doses in subject P. H. was only one second greater than the range of variation after duplicate measurements with the same dose (see Table II).

†Normal in the sense defined by Robb and Weiss.³

TABLE II

DUPLICATE MEASUREMENTS OF PAPAVERINE CIRCULATION TIME

SUBJECT	DOSE OF PAPAVERINE MG.	TIME OF END POINT SEC.	DIFFERENCE SEC.
1. H. P.	40	24.2	0.6
	40	24.8	
2. I. K.	40	22.4	0.4
	40	22.0	
3. M. L.	40	19.4	1.6
	40	21.0	
4. C. W.	32	25.4	0.6
	32	26.0	
5. M. W.	40	18.0	0.6
	40	17.4	
6. H. L.	40	27.0	2.0
	40	25.0	
7. J. LaF.	40	21.2	0.4
	32	21.6	
8. S. R.	40	15.4	1.0
	40	16.4	
9. T. F.	64	17.2	0.8
	64	18.0	
10. V. W.	64	17.5	1.5
	64	19.0	
11. I. V.	40	26.8	1.3
	40	25.5	
12. A. W.	40	18.6	2.4
	48	21.0	
13. H. C.	64	17.2	3.0
	64	20.2	
14. R. R.	40	21.6	0.6
	40	21.0	
15. F. D.	40	20.8	0.4
	40	20.4	
16. H. M.	32	19.2	1.4
	48	20.6	
17. J. D.	48	17.6	1.0
	56	16.6	
18. H. W.	32	17.8	1.2
	48	19.0	
19. E. L.	32	17.4	1.4
	48	18.8	
20. H. W.	40	20.2	1.2
	40	21.4	
21. W. R.	40	26.8	0
	40	26.8	
22. W. D.	40	17.0	2.0
	40	19.0	
23. J. M.	40	17.0	1.2
	40	18.2	
24. P. H.	40	24.2	0.6
	40	24.8	

Range of variation between two successive readings is 0 to 3.0 sec.
Average difference is 1.2 sec.

the papaverine circulation time, as well as the decholin time, was markedly prolonged. Patient R. C. was of particular interest. His papaverine circulation time when he did not have failure was 18.4 seconds. One month later he developed dyspnea, orthopnea, cyanosis, and basal râles, indicating acute heart failure. The papaverine test at this time revealed a circulation time of 60 seconds (the decholin time was 33 seconds); this confirmed the diagnosis of heart failure. The papaverine circulation time in hyperthyroidism is shortened, but the deviation from normal is not as marked as its prolongation in heart failure.

TABLE III
CIRCULATION TIME IN CONGESTIVE HEART FAILURE

PATIENT	ETIOLOGIC DIAGNOSIS	RESPIRATORY RATE PER MIN.	PULSE RATE PER MIN.	TEST SUBSTANCE	TIME OF END POINT SEC.
1. S. R.	Syphilitic heart disease	30	92	Papaverine	50.2
2. W. H.	Rheumatic and hypertensive heart disease	20	80	Papaverine Decholin	38.6 30.8
3. J. C.	Syphilitic heart disease	38	112	Papaverine Decholin	48.0 30.8
4. T. G.	Possibly beriberi heart disease	38	80	Papaverine Decholin	115.8 63.6
5. F. M.	Arteriosclerotic heart disease	22	92	Papaverine	60.4
6. R. C.*	Arteriosclerotic heart disease	32	92	Papaverine Decholin	60 33

*Discussed in text.

Range of papaverine circulation time is 38.6 to 115.8 sec.

Range of decholin circulation time is 30.8 to 63.6 sec.

TABLE IV
CIRCULATION TIME IN HYPERTHYROIDISM

PATIENT	BASAL METABOLIC RATE	PULSE RATE PER MIN.	TEST SUBSTANCE	TIME OF END POINT SEC.
1. I. S.	+26	108	Papaverine	13.3
2. L. D.	+6	100	Papaverine Decholin	13.8 8.8
3. R. P.	+19	132	Papaverine	13.4
4. L. B.	+34	100	Papaverine	11.7

The results obtained with papaverine in the control series were compared with those of a subjective test, in which 4 or 5 c.c. of a 20 per cent calcium gluconate* solution were used; this test was done either shortly before or after the papaverine test, or within one to two days of the latter. The values obtained in 18 patients are presented in Table V, which shows that the calcium gluconate circulation time differs from the papaverine time by 0.6 to 12.4 seconds. The fact that

*Neo-CaIglucon, which was kindly supplied by Sandoz and Company.

the former estimations are within the normal range further indicates that there was no circulatory failure in the patients studied.

TABLE V
COMPARISON OF PAPAVERINE AND CALCIUM CIRCULATION TIMES

SUBJECT	TEST SUBSTANCE	TIME OF END POINT
1. S. R.	Papaverine	15.9
	Calcium	13.7
2. P. H.	Papaverine	24.8
	Calcium	18.0
3. J. D.	Papaverine	17.6
	Calcium	14.0
4. E. M. L.	Papaverine	17.4
	Calcium	12.8
5. A. T.	Papaverine	21.8
	Calcium	12.4
6. C. M.	Papaverine	20.6
	Calcium	20.0
7. H. W.	Papaverine	18.4
	Calcium	15.4
8. D. D.	Papaverine	27.0
	Calcium	19.4
9. J. D.	Papaverine	15.4
	Calcium	11.2
10. H. Y.	Papaverine	15.8
	Calcium	9.0
11. J. T.	Papaverine	20.8
	Calcium	18.2
12. E. S.	Papaverine	21.2
	Calcium	12.6
13. W. N.	Papaverine	19.2
	Calcium	15.0
14. F. K.	Papaverine	22.0
	Calcium	13.4
15. S. B.	Papaverine	25.4
	Calcium	15.0
16. E. C.	Papaverine	25.0
	Calcium	16.0
17. M. G.	Papaverine	16.0
	Calcium	10.6
18. J. M.	Papaverine	26.2
	Calcium	13.8

Range of papaverine circulation time is 15.4 to 27.0 sec.

Range of calcium circulation time is 9.0 to 20.0 sec.

Range of difference between papaverine and calcium times is 0.6 to 12.4 sec.

Average difference between papaverine and calcium times is 6.1 sec.

DISCUSSION

Robb and Weiss³ have clearly defined the requisites of any agent which is given intravenously as a measure of circulation time, namely,

it should be nontoxic in the doses employed; it should not influence the velocity of blood flow until the signal reaction has occurred; it should be quickly inactivated, so that a second measurement may be made within a few minutes; and the end point should be easily recognized. Our results show that papaverine adequately fulfills these requirements.

Papaverine hydrochloride has the advantage over sodium cyanide of being readily available in known concentrations in sterile solution, and the small volume of solution which is used can be rapidly administered.

In addition to this, papaverine hydrochloride has been used therapeutically in the treatment of conditions associated with smooth muscle spasm, as, for example, pulmonary embolism⁸ and peripheral embolism.⁹ Furthermore, work on animals in this laboratory has shown that papaverine hydrochloride is a potent and lasting coronary dilator,⁴ that it can prevent or reduce artificially induced ventricular fibrillation,⁵ and that it will abolish or diminish artificially induced ventricular premature systoles in the dog.⁶ We have applied this information clinically⁷ and have found that when this drug is given intravenously or orally it is efficacious in the treatment of the anginal syndrome and of premature systoles. Papaverine can also be administered intravenously as a temporary measure to abolish or reduce single or multiple ectopic premature contractions.⁷ Thus, our evidence indicates that this drug may be employed intravenously for simultaneous measurement of the circulation time and attainment of some therapeutic effect which might be desired, as, for example, in pulmonary embolism. We are not aware of any therapeutic possibilities possessed by sodium cyanide.

Robb and Weiss³ concluded, from indirect evidence in man and more direct evidence in animals, that sodium cyanide acts on the carotid sinus, and hence gives a measure of the arm-carotid sinus time. The fact that the range of our measurements, as well as the average for papaverine, is longer than that obtained with the sodium cyanide method by about five to six seconds suggests the following possibilities:

1. Papaverine has a slower effect on the carotid sinus in the dosage recommended.
2. It acts on a center more distal from the heart than the carotid sinus, i.e., the respiratory center in the medulla.

We are not acquainted with any work on the action of papaverine on the carotid sinus in animals. Macht¹⁰ has said that papaverine apparently stimulates the respiratory center in the intact, unanesthetized rabbit. Our results with papaverine are nearer the values obtained with the histamine circulation time test (thirteen to thirty seconds, average twenty-three seconds³) than those with the cyanide method. Histamine³ is believed to cause dilatation of the smaller blood vessels of the skin and brain. As previously mentioned, papaverine commonly causes visible flushing of the face. Hence, the evidence, although indi-

rect, suggests that this drug acts on a site beyond the carotid sinus, possibly on the blood vessels of the brain, or, more likely, on the respiratory center. Accordingly, for the present, at least, papaverine may be considered to offer a measure of the arm-respiratory center circulation time.

SUMMARY

1. A new, simple, reliable, and objective method, which utilizes papaverine hydrochloride intravenously, is described for the measurement of circulation time. The end point consists of a sudden, deep inspiration.

2. The recommended dose is 40 mg. (1.25 c.c.). The average time for 50 normal persons without evidence of heart failure was 20.8 seconds; the range extended from 15.4 to 27.0 seconds.

3. Duplicate measurements may be made within 2 to 5 minutes; the estimations varied by no more than 3 seconds, and the variations averaged 1.2 seconds.

4. Indirect evidence suggests that papaverine hydrochloride may measure the arm-respiratory center circulation time.

5. Whenever papaverine is given intravenously for therapeutic reasons, the circulation time may readily be measured simultaneously by means of the above technique.

It is a pleasure to acknowledge the advice and criticism of Dr. Louis N. Katz, under whose guidance this study was carried out.

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Clinical Reports

COARCTATION OF THE AORTA, WITH RUPTURE OF THE WALL BELOW THE POINT OF CONSTRICTION

REPORT OF A CASE AND REVIEW OF THE LITERATURE

VICENTE MORAGUES, M.D., LOUIS T. MOORE, M.D., AND
JULIUS A. ROSSEN, M.D., St. Louis, Mo.

IN ABBOTT'S¹ series of 200 cases of the adult type of coarctation and in Benkwitz and Hunter's² series of 75 cases (52 of adult type), the causes of death were: (1) cardiac decompensation, 38 per cent; (2) rupture of ascending aorta, 17 per cent; (3) cerebral lesions, 13 per cent; and (4) mycotic endarteritis, 7 per cent. In the two series combined, there were only three cases of rupture of the aorta below the constriction. Goodson,³ in 1937, and Hecker,⁴ in 1939, reported two more cases of coarctation of the aorta with rupture of the wall below the site of coarctation. Thus, in all, five cases of coarctation of the aorta, with rupture of the wall below the point of constriction, have been reported. We present another case of the same type in which there were some other interesting features.

CASE REPORT

An eleven-year-old boy was admitted to the hospital with complaints of hematemesis, dyspnea, and precordial pain.

He had measles at the age of three, but no other illnesses, accidents, or operations. The family history was negative. The boy was born at full term; delivery was easy, and growth and development had been normal.

The boy was in good health until three months before admission, when he noticed increasing dyspnea and was forced to curtail his exercise and finally stop playing entirely. He had an occasional cough and a small amount of sputum. In spite of medication he became worse, with excessive dyspnea, frequent cough, and difficulty in sleeping. One week before admission he suddenly became worse and complained of precordial pain and orthopnea. His sputum was consistently free of blood and was described as a "phlegm." The night before admission he awoke at 10:00 o'clock and vomited a large amount of coffee-ground material. Later he spat up a quantity of bright red blood. At 4:00 A.M. he again vomited blood and became unconscious. He passed a large black stool.

Physical Examination.—The patient was a well-developed but rather poorly nourished boy who appeared acutely ill. He had marked dyspnea and a remarkable pallor of the face. The hands were cold and clammy and the pulse was extremely rapid (170). Examination of the head, eyes, ears, and nose was negative.

From the Departments of Pathology and Pediatrics, Saint Louis University School of Medicine.
Received for publication June 30, 1941.

There was marked pallor of the buccal mucous membrane. The chest was sthenic in type and breathing was rapid. Sibilant râles were heard throughout the chest, both on inspiration and expiration. The breath sounds were bronchovesicular. Percussion was resonant throughout. The heart rate was 170 per minute and the rhythm was normal. The apex impulse was diffuse, and the outer border of cardiac dullness was in the fifth intercostal space, $8\frac{1}{2}$ cm. from the midline. There was a loud systolic murmur in the aortic area, transmitted to the great vessels, and a soft systolic murmur in the mitral area, transmitted to the axilla. There was reduplication of both aortic and pulmonic second sounds. The abdomen was scaphoid and tender throughout. The liver was palpable two cm. below the costal margin, and the spleen was thought to be palpable. The extremities showed no edema, and the reflexes were normal.

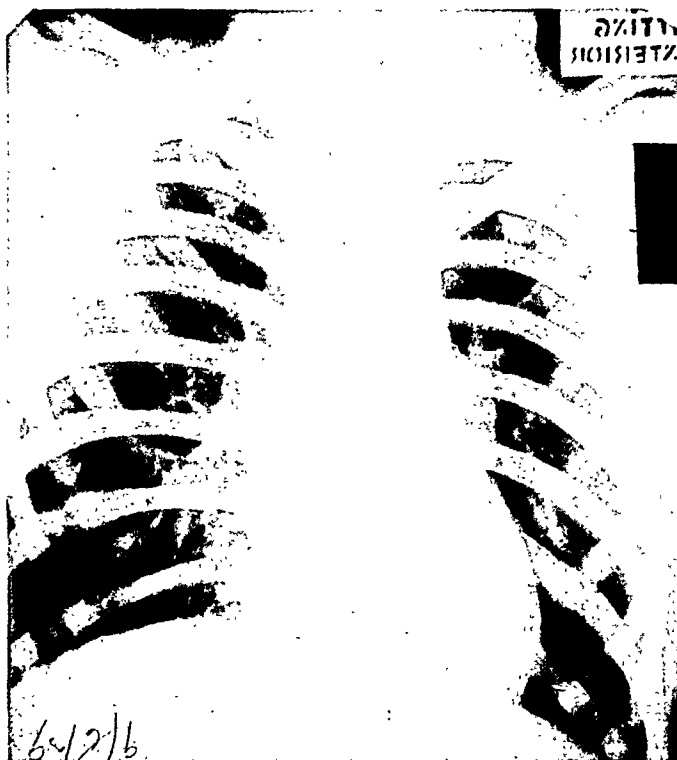


Fig. 1.—Roentgenogram of chest, showing absence of aortic knob and broadening of the aortic arch.

Laboratory Data.—The erythrocyte count was 3,310,000, the hemoglobin, 49 per cent, the leucocyte count, 35,000, and the platelet count, 299,700. The differential leucocyte count showed 3 per cent metamyelocytes, 30 per cent nonsegmented forms, 59 per cent segmented forms, 7 per cent lymphocytes, and 1 per cent monocytes. The blood sugar level was 100 mg. per cent, and the nonprotein nitrogen content of the blood was 37 mg. per cent. The blood Kahn and Kline reactions were negative. A stool culture was negative for the typhoid and dysentery group.

Roentgenologic examination of the chest showed no enlargement of the heart, but a slight broadening of the aortic arch. The lungs appeared normal (Fig. 1). The electrocardiogram showed: (1) sinus tachycardia; (2) right axis deviation; and (3) evidence of myocardial and auricular disease.

Course in Hospital.—The second day the temperature was 99° F. The patient received a transfusion of 150 c.c. of whole blood and felt better; he passed a bloody stool. The blood pressure was 155/80.

On the morning of the third day he appeared improved, had better color, and wanted to get up and walk about. Examination of the chest revealed some increase in the width of the area of aortic dullness. The blood pressure in the left arm was 150/95; and, in the right arm, 145/80. The pulse rate was 100.

In the afternoon of the third day a sudden, massive hemorrhage occurred; blood poured from the mouth and nose. He rapidly went into shock and died before any effective treatment could be administered.

Autopsy.—The body was that of a well-developed, somewhat undernourished boy of eleven years; the skin was pale, with a slight yellowish cast. No gross lesions or abnormalities were noted on external examination of the body. There was a moderate amount of thin, straw-colored fluid in both pleural cavities and in the pericardial cavity.

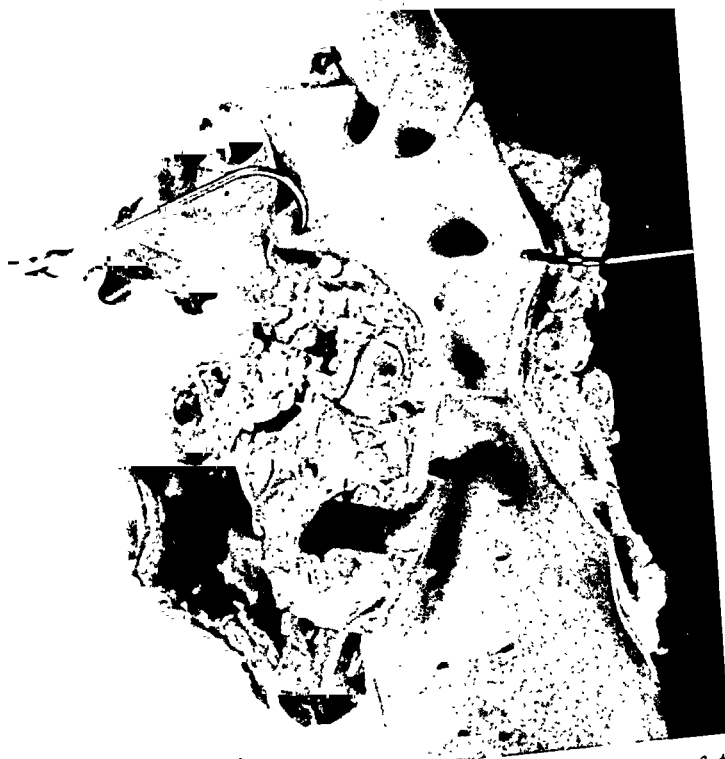


Fig. 2.—Marked coarctation of the aorta at the site of insertion of the ligamentum arteriosum. Anomalous vessel between the left subclavian artery and the constriction.

The heart was somewhat enlarged, particularly the left ventricle. The epicardium was thin and intact. The myocardium was pale and somewhat thickened in the left ventricle. The valves and coronary arteries were not abnormal.

Aorta.—In the aorta, one inch below the origin of the left subclavian artery, there was a marked and circumscribed narrowing of the lumen to a diameter of about 5 mm. This narrowing was at the site of insertion of the ligamentum arteriosum, which was present as a thick fibrous cord 1 cm. long. There was an anomalous vessel, 2 mm. in diameter, in the anterior wall of the aorta and 1 cm. below the left subclavian artery (Fig. 2). Just below the coarctation there was an aneurysmal dilatation along the anterior wall of the aorta, with rupture into the esophagus. On the line of rupture there was a vegetation 3 mm. long, and, in the opening, there was a large, partially organized thrombus that protruded into the esophagus (Fig. 3). The lungs revealed some hypostatic congestion and the gastrointestinal tract contained a large amount of dark, partially digested blood.

Microscopic Examination.—Sections from the aorta at the site of rupture showed a vegetation formed by fibrin, inflammatory cells, and granulation tissue, but no bacteria were present. The layers of the wall showed infiltration with inflammatory cells, mostly neutrophils and monocytes. The thrombus between the aorta and esophagus showed partial organization, with many fibroblasts throughout. The heart muscle showed some edema and also hyperplasia of the fibers. Moderate congestion and edema were present in the lungs. The kidneys revealed lesions of an embolic type, with localized collections of inflammatory cells around some of the glomeruli, and also some glomeruli with obliteration of Bowman's capsule.



Fig. 3.—Large thrombus protruding into the esophagus through a break in the mucosa.

The five cases of coarctation of the aorta, with rupture of the wall below the point of constriction, that have been previously published are summarized here briefly. The description of the first three cases⁵⁻⁷ is taken from Abbott.¹

Leudet,⁵ in 1858, reported the case of a woman, thirty-seven years old, who had had dyspnea, dysphagia, pain in the left side of the chest, and edema of the extremities for nineteen months. She died suddenly after vomiting a large quantity of blood. The descending aorta just below the origin of the left subclavian was so extremely constricted that it would admit only a blunt probe, and, just below this point, presented a huge, irregular, aneurysmal dilatation lined by osseous and car-

filaginous plaques which opened freely into the left bronchus. A good collateral circulation was present, and also some enlargement of the left ventricle.

In 1878, Kriegk⁶ published the case of a university professor, aged forty-eight, who had suffered for several years from precordial pain and anxiety; he died suddenly while going to bed. The autopsy revealed much blood in the mediastinum and in the left pleura. At the site of entrance of the obliterated duct, the descending aorta was narrowed by an annular constriction which admitted the little finger. On either side of this constriction there was a double intimal tear. The tear above the stenosis was 1.5 cm. long and ran around the aorta parallel to the ridge; that below was of similar length and course and led into a dissecting aneurysm which had extended downward as far as the celiac axis; both tears had ruptured near their origin into the mediastinum and adjacent structures.

In 1907, Mönckeberg⁷ presented the case of a woman, aged twenty-six, with congenital hypoplasia of the aorta. The aorta narrowed rapidly distal to the origin of the innominate artery and became reduced at the insertion of the obliterated ductus to a circumference of 1.3 cm. Just below the stenosis there began an aneurysmal dilatation which bulged into the left lung; it measured 8 cm. in its greatest vertical diameter. The ligamentum arteriosum was a solid cord, 1.5 cm. long, attached to the floor of a funnel-shaped, loculated pocket which had perforated into the left pleura. There was a large collateral circulation.

Goodson,³ in 1937, recorded the case of a boy, sixteen and a half years old, who had had dyspnea and precordial pain for two months before entering the hospital. He died suddenly, three weeks later, after having expectorated bright red, frothy blood on several occasions. The autopsy revealed narrowing of the descending arch of the aorta to 1 cm. at about 1 cm. above the insertion of the ductus arteriosus, which was patent for about half its length. Immediately below this insertion there was a fibrous constriction of the aortic wall to a lumen 3 mm. in diameter. Two centimeters below the coarctation there was an 8 mm. opening into an aneurysm which was situated on the left of the midline between the fifth and sixth ribs and measured 3.5 by 3.5 by 4 cm. It was partly filled with organizing clot and had ruptured into a small bronchus.

In 1939, Hecker⁴ reported the case of a man, sixty-two years old, who had had hypertension for years. After a strenuous movement to prevent falling from his seat, he suddenly developed a severe, lancinating pain in the back. He died two weeks later of self-inflicted gunshot wounds. The autopsy revealed a marked constriction of the descending arch of the aorta one and one-half inches beyond the origin of the left subclavian artery. At this point a ligamentous attachment, about one-fourth to one-half inch in width, extended to the pulmonary artery. The lumen

of the aorta at the coarctation was about 2 mm. in diameter. Immediately below this point the aorta became enlarged and bulbous. About six inches below the constriction there was a longitudinal slit through the posterior wall of the aorta. Through this opening the blood had dissected between the walls of the aorta upward to the constriction and downward to within about one and one-half inches of the bifurcation of the abdominal aorta.

DISCUSSION

In the case that we have presented here, as in that of Hamilton and Abbott,⁸ there was an anomalous vessel between the origin of the left subelavian artery and the site of coarctation. We agree with Hamilton and Abbott that an anomalous vessel in this location lends support to the views of Reynaud,⁹ Rokitansky,¹⁰ and Loriga,¹¹ to the effect that coarctation is caused by an abnormal development during embryonic life, localized at the point of junction of the fourth, fifth, and sixth left aortic arches. The anomalous vessel would represent persistence of the (evanescent) fifth left arch.

Rupture of the ascending aorta is much more common in coarctation than rupture of the wall below the constriction. This can be easily explained by the fact that the blood pressure is much higher above than below the constriction. The explanation of rupture below the site of coarctation may be found in a certain weakening of the wall near that point. We believe, however, that back pressure from some strain, with or without contraction of the abdominal muscles, will give a very marked rise in blood pressure against a rather rigid wall near the site of coarctation and may produce a tear of the wall. Hecker's⁴ case seems to illustrate this back pressure idea.

SUMMARY

1. A case of coarctation of the aorta, with rupture of the wall below the point of constriction, into the esophagus, is presented.
2. The five previously published cases of coarctation with rupture of the wall below the constriction are reviewed.
3. We believe that back pressure plays an important role in the mechanism of rupture of the wall below the site of coarctation.

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THE PERIPHERAL BLOOD FLOW IN A CASE OF ADRENAL PHEOCHROMOCYTOMA BEFORE AND AFTER OPERATION

WILLIS F. EVANS, M.D.,* AND HAROLD J. STEWART, M.D.
NEW YORK, N. Y.

THE clinical diagnosis of adrenal pheochromocytoma has been made with increasing frequency during recent years. The syndrome associated with the paroxysmal hypertension of adrenal medullary tumors was first clearly described by Labbe, Tinel, and Doumer, in 1922.¹ Beer, King, and Prinzmetal² demonstrated during the hypertensive crises the presence of a circulating pressor substance, and identified it as adrenalin. This substance was no longer present after operation. Landis, Montgomery, and Sparkman³ found that the intravenous administration of epinephrine was followed by an elevation of blood pressure, a decrease in peripheral blood flow and skin temperature, and an increase in peripheral resistance.

We have had the opportunity to make measurements of the peripheral blood flow before operation and on several occasions after operation on one patient with a chromaffin cell tumor of the adrenal medulla;† such observations have not previously been recorded. In order to have other data for correlation in this patient, the basal metabolic rate, blood pressure, pulse rate, and circulation time (arm-to-tongue) were also measured.

CASE REPORT

History.—D. K., History No. 254438, a colored girl, aged 14 years, was admitted to the Medical Service of the New York Hospital January 6, 1940, with the chief complaint of blurring of vision of five months' duration.

Present Illness.—Three years prior to admission, the patient first noticed the onset of weakness and sweating. These attacks gradually became more frequent. They were not associated with fever. Approximately one year before admission the patient began to have dyspnea on climbing one flight of stairs, a preference for sleeping on two pillows, and moderate polydipsia and polyuria. Severe bitemporal headaches of relatively short duration and sudden onset of blurring of vision began in July, 1939. About this time sweating became more profuse. In September, 1939, the patient's mother observed puffiness of the eyelids and swelling of the feet, and the patient began to complain of transient, sudden coldness of the hands and feet. Approximately two weeks before admission, there was a short period of tinnitus. There was no history of convulsions, syncope, memory loss, or disorientation.

From the New York Hospital and the Department of Medicine, Cornell University Medical College, New York, N. Y.

Received for publication July 3, 1941.

*Lewis Cass Ledyard Fellow in Medicine, 1940-1941.

†The surgical aspects of this case are to be published from the New York Hospital and Department of Surgery, Cornell University Medical College, New York, N. Y.

Physical Examination.—The patient did not appear acutely ill. The temperature (rectal) was 37.4° C. The pulse and respiratory rates were 132 and 20 per minute, respectively. The blood pressure (right arm) was 210/120. The skin over the feet, legs, and hands was reddish, dry, and thickened, and appeared smooth and atrophic. There was profuse sweating over the trunk. The muscular development was poor. Examination of the eye grounds showed widespread edema about the left disc, which was almost totally obscured, and diffuse scarring and a few small, fresh hemorrhages of the retina were observed. The right fundus showed recent hemorrhages in the nasal field and fresh "cotton patches" of exudate in the temporal field and about the disc. The latter was almost invisible. There were many small, streak hemorrhages along the vessels. The arterioles bilaterally were extremely spastic. The heart was markedly enlarged; a diffuse, heaving impulse extended 10 cm. to the left of the midsternal line in the fifth intercostal space. Pulsus alternans was present. The heart sounds were loud. A protodiastolic gallop was heard at the apex. A rough systolic murmur was heard over the pulmonic area and down the left border of the sternum. The aortic second sound was accentuated. The pulsations in the two dorsalis pedis arteries were difficult to feel. The right kidney was readily palpated but appeared to be normal in size.

Preoperative Laboratory Data.—The range in specific gravity of the urine was 1.012 to 1.030. The amount of albumin varied from none to 2 plus. Occasional erythrocytes and granular casts were seen in the sediment. The blood cholesterol was 289 mg./100 c.c. On two occasions the serum protein was 7.8 and 5.7 mg./100 c.c., respectively. On three occasions the urea nitrogen was 16, 12, and 8 Gm./100 c.c., respectively. The phenolsulphonphthalein test showed a total dye output of 72.5 per cent in two and one-half hours. The urea clearance was 92 and 81 per cent, respectively, on different occasions. The fasting blood sugar was 82 mg. per cent. One-half hour after the ingestion of 100 gm. of glucose it was 138 mg. per cent, one hour afterward, 194 mg. per cent; it was 156 mg. per cent at the end of two hours, and 130 mg. per cent at the end of three hours. All of the urine specimens during this test were negative for sugar except the second, which showed 1+ sugar. The creatine tolerance test showed a retention of 34.8 per cent. The serum chlorides were 93.4 and 88.0 millimolar equivalents per liter. The serum potassium was 4.3 millimolar equivalents per liter. The serum sodium was 135 millimolar equivalents per liter. The prothrombin was 100 per cent of normal. The basal metabolic rate was +46 per cent, +43 per cent, and +48 per cent, respectively, on different days.

Course.—The ease with which the right kidney was palpated, the general clinical picture, and the fluctuations in blood pressure (150 to 250 mm. Hg, systolic, and 118 to 160 mm. Hg, diastolic) suggested the possibility of an adrenal tumor. In order to explore this possibility, urograms were made January 18, 1940. The kidneys showed normal function. The superior calyx in the upper pole of the right kidney was deviated laterally. In the region of the right adrenal gland a small, irregular, calcific area was seen. On January 27, 1940, perirenal insufflation of CO₂ into the right adrenal area was carried out. Roentgenograms showed a large, rounded shadow of increased density, approximately 6 cm. in diameter, in the region of the right adrenal. The calcification was seen to lie within this shadow. A diagnosis of right-sided adrenal tumor was made. Pneumoradiographic examination of the left kidney region showed that the left adrenal was normal in size, shape, and position. Studies of the peripheral blood flow, basal metabolic rate, pulse rate, blood pressure, and circulation time were made the morning of February 4, 1940. The patient was transferred to the Surgical Service February 7, 1940. Before removing the tumor, surgical exploration of the left adrenal region was carried out February 20, 1940, and revealed a normal adrenal gland on that side. The convalescence from this operation was uneventful. The patient continued to suffer from

headaches and sweating. On the evening of March 4, 1940, she experienced persistent cough, tachycardia, rapid respirations, and profuse sweating. There were moist râles over the lower halves of both lungs. The blood pressure was 250/150. These alarming signs rapidly subsided, and later in the day the blood pressure was 190/140, with only a few râles at the bases. The blood pressure the following morning was recorded as 170/120. It was our impression that the patient had suffered from a hypertensive crisis, with pulmonary edema. Because of this attack, rapid digitalization was undertaken at once, and the patient was given maintenance amounts of digitalis. On March 7, 1940, adrenalectomy was carried out on the right side, and an adrenal tumor, measuring $5\frac{1}{2} \times 4\frac{1}{2} \times 4$ cm. and weighing 63.5 grams, was removed. During the operation a small nick was made in the pleura, causing right-sided pneumothorax. This was promptly closed. A transfusion was started at the completion of the operation, and the patient was returned to the pavilion in excellent condition. The pathologic diagnosis of this tumor was pheochromocytoma of low-grade malignancy. Biologic assay showed adrenalin-like effects when one cubic centimeter of the filtered saline extract of a portion of the tumor was slowly injected intravenously into a twenty-three-pound dog.* For the first few postoperative days, there was respiratory distress associated with the pneumothorax. Aspiration of air and an oxygen tent afforded relief. Roentgenograms taken March 22, 1940, showed practically complete expansion of the right lung. Postoperative excretion urograms showed that the renal shadows were normal. The right kidney now appeared to be in its normal position. After the operation the patient was free of headache, weakness, dizziness, sweating, polydipsia, and polyuria. On March 25, 1940, postoperative measurements of the peripheral blood flow, basal metabolic rate, pulse rate, blood pressure, and circulation time were again made. During the last ten days of her hospital stay the patient gained six pounds in weight. The average blood pressure was 117/73, and the pulse rate ranged usually from 80 to 90 per minute during the postoperative period. The patient was discharged twenty-six days after operation in excellent general condition. At this time the operative wounds were well healed. The use of digitalis, 0.1 Gm. daily, was continued.

Postoperative Laboratory Data.—The range of the specific gravity of the urine was from 1.015 to 1.030. The albumin varied from negative to one plus. Occasional erythrocytes and a few leucocytes were observed in the sediment. The hemoglobin was 13.5 Gm. (92 per cent). The erythrocyte count was 4.9 million. The serum chlorides on two occasions were 560 and 600 mg. per cent. The serum calcium was 11.7 mg. per cent. The creatine tolerance test showed a retention of 83.7 per cent. The basal metabolic rate was -17 per cent. Before operation the electrocardiogram showed slight left axis deviation, probably as a result of the hypertension. The low amplitude of T_1 , together with the fact that T_2 and T_3 were diphasic, indicated myocardial damage. After the administration of digitalis, T_1 became negative, T_2 changed form, and T_3 became upright. On June 15, 1941, three months after operation and one month after discontinuing digitalis, the left axis deviation had disappeared and the T waves had all become upright and had a normal contour. On the whole, the electrocardiogram had a normal configuration.

Course After Leaving Hospital.—Studies of peripheral blood flow, basal metabolic rate, pulse rate, and blood pressure were repeated May 3, 1940. Digitalis was discontinued at this time. Studies of the peripheral circulation were carried out November 9, 1940, and again on March 22, 1941. The patient has been observed at intervals since discharge from the hospital. She has been free of complaints. The blood pressure and pulse rate have been normal during each observation. She has

*We wish to thank Dr. Frank Glenn, of the Department of Surgery, for permission to use these data.

gained weight. There has been slight progressive improvement in eyesight, and objectively the fundi show some peripheral clearing. She has gradually returned to a normal amount of physical activity and resumed work at school.

METHODS

The method used by Stewart and Jack⁴ and Stewart and Evans^{5,6} in earlier measurements of peripheral blood flow was employed. This method requires the accumulation of certain data, namely, measurements of skin temperature, for which the Hardy-Soderstrom improved radiometer was used,⁷ and measurements of rectal temperature, oxygen consumption, height, and body weight. The order in which data were collected has already been described^{5,6}. All observations were made with the patient in a basal metabolic state. Six sets of skin temperature readings from eleven areas of the body and of rectal temperature measurements were taken at twenty-minute intervals. From these recordings, five average periods of peripheral blood flow were calculated. The pulse rates and blood pressures were also recorded. The arm to-tongue circulation time (Decholin's) was measured after the last estimation of oxygen consumption. The same sequence of observations was followed in the postoperative as in the preoperative studies, and the same environmental temperature was used.^{5,6} Data were collected once before, and on four occasions after, operation.

RESULTS

Basal Metabolic Rate and Peripheral Blood Flow.—Before operation, when the basal metabolic rate was increased to +48 per cent, the peripheral blood flow was only 59 c.c./M²/min. After operation the basal metabolic rate fell to -17, -13, -16, and -13 per cent, respectively, yet there were increases in peripheral blood flow to 90, 94, 92, and 99 c.c./M²/min., respectively. There was, therefore, a marked relative increase in peripheral blood flow during the postoperative period, at a time when there was a fall in the basal metabolic rate to normal (Table I) (Fig. 1).

Skin Temperature.—Before operation the average skin temperature was low. After removal of the tumor the average skin temperature was approximately 1° to 1½° C. higher. The temperature of the hands and feet showed trends similar to average skin temperature in both the preoperative and postoperative phases. There was, however, no constant relationship between average skin temperature and the temperature of the extremities during a morning's observations (Table I) (Fig. 1).

Rectal Temperature.—At first, when the average skin temperature was decreased (32.45° C.), the rectal temperature was elevated (37.93° C.). After operation the rectal temperature was normal during each of the observations, at a time when the average skin temperature had risen to normal (Table I) (Fig. 1).

Pulse Rate.—Tachycardia was present before operation, but the rate fell to normal after removal of the tumor (Table I) (Fig. 1).

Blood Pressure.—The systolic and diastolic pressure was markedly elevated before operation and fell to normal after operation (Table I) (Fig. 1).

TABLE I
AVERAGE VALUES OF MEASUREMENTS ON D. K.

		BEFORE OPERA- TION	AFTER OPERATION			
			18 DAYS	2 MONTHS	8 MONTHS	1 YEAR
Digitalized		No	Yes	Yes	No	No
Basal Metabolic Rate	Per Cent	+48	-17	-13	-16	-13
Peripheral Blood Flow	C.c./M ² /Min.	59	90	94	92	99
Circulation Time	Seconds	11.3	-	-	13.6	13.8
Blood Pressure	Mm. Hg	190/130	120/84	118/80	98/54	98/64
Pulse Rate	Per Min.	138	82	72	70	60
Average Skin Temp.	Degrees C.	32.45	33.60	34.23	34.20	34.08
Average Hand Temp.	Degrees C.	31.10	32.90	34.20	34.20	33.30
Average Foot Temp.	Degrees C.	26.80	27.50	33.20	28.60	29.50
Average Rectal Temp.	Degrees C.	37.93	36.93	37.26	37.27	37.03
Heart Area	Sq.Cm.	99.1	103.8	-	100.9	-

DISCUSSION

The objective measurements now being reported show that there was, relatively, a marked decrease in peripheral blood flow when patient D. K. was suffering from an adrenal pheochromocytoma, for the peripheral blood flow was only 59 c.c./M²/min. at a time when the basal metabolic rate was increased to +48 per cent. After operation, although the metabolic rate decreased to a normal level, there was an average increase of 60 per cent in the amount of blood allotted to the peripheral circulation (Table I) (Fig. 1). Stewart and Evans⁵ showed that, at a similar environmental temperature, patients suffering from hyperthyroidism with basal metabolic rates comparable to the preoperative level of subject D. K. had a peripheral blood flow of approximately 225 c.c./M²/min. After operation, when these same subjects were within the normal metabolic range, the average peripheral blood flow was approximately 70 c.c./M²/min. Comparing these data for the two diseases, it is evident that subject D. K. had a marked reduction in peripheral blood flow at a time when the oxygen consumption might require it to be greater. Perfusion experiments, made with an extract of the tumor, showed that it contained an adrenalin-like substance. It is proper to assume, therefore, that it was this substance, elaborated by the tumor, which induced these circulatory phenomena in this patient. It is known that one of the actions of epinephrine is to decrease peripheral blood flow. After removal of the tumor the basal metabolic rate decreased and peripheral blood flow increased.

The elevated heat production attendant upon increased oxygen consumption usually brings about a high skin temperature.⁵ In subject D. K., the average skin temperature before operation was low at a time when the basal metabolic rate was high. After operation it increased to normal. Vasoconstriction is one of the actions of epinephrine. Low skin temperature was to be anticipated before operation, therefore, because peripheral vasoconstriction and decreased peripheral blood flow were present during hyperadrenalemia. As a consequence, the skin

could not dissipate efficiently the increased amount of heat produced, and increased heat storage and a high rectal temperature resulted. At this point it may be of interest to speculate upon the mechanism of the attacks of profuse perspiration which occurred before operation. There is reason for the opinion that they were not initiated entirely by direct sympathetic stimulation of the sweat glands by adrenalin, for they occurred in attacks. If there was an increased amount of circulating adrenalin at the time of sweating, an additional elevation of blood pressure would be expected also. There were no unusual rises in blood pressure or hypertensive crisis during these attacks while the patient was under observation, except for the one instance mentioned in the case report. Another explanation which appears most applicable is that the heat regulating center, finding the internal temperature (rectal) too high, responded by calling for profuse perspiration intermittently in order to bring into action the cooling effect of evaporation.

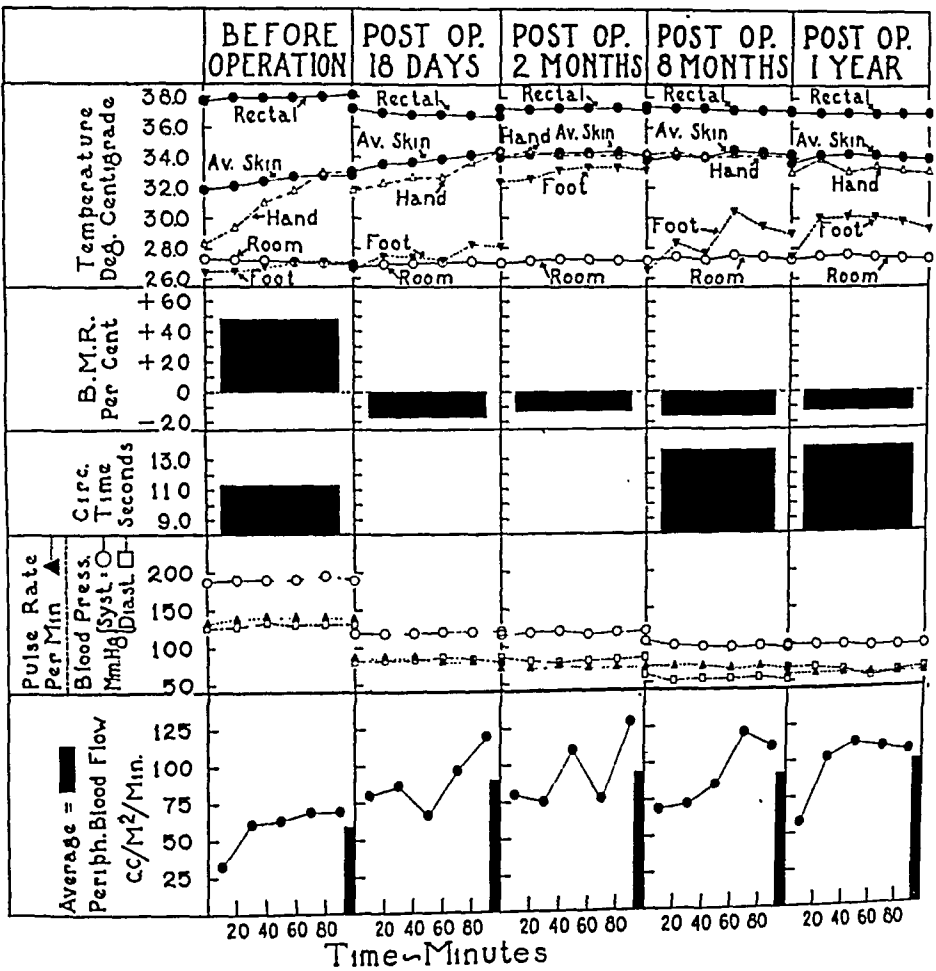


Fig. 1.

The temperature of the hands and feet showed trends similar to average skin temperature in both the preoperative and postoperative phases. There was no constant relationship between average skin temperature and the temperature of the extremities during a morning's observations.

Fatherree and Allen,⁹ in observations on the vasoconstrictor effects of epinephrine on the digital arterioles, found a more prolonged action in the toes than in the fingers. Moreover, they were of the opinion that the vasoconstrictor action in normal persons may vary widely, giving rise to marked variability in the skin temperature of different digits, and in the same digit at different times in the same subject. To some extent, the results in this patient (Table I) (Fig. 1) parallel those obtained by Fatherree and Allen.⁹ Hardy¹⁰ found, in subjects who were receiving an infusion of epinephrine, a marked fall in the skin temperature and peripheral blood flow of the extremities at the same time that the average skin temperature and average peripheral blood flow were increased. Before operation in our case, not only the temperatures of the extremities, but also the average skin temperature and average peripheral blood flow of the whole body surface were decreased. These observations are not at variance with the work of Hardy, for it is well known that the pharmacologic action of smaller amounts of adrenalin will be primarily reflected in the extremities, whereas, with larger amounts, the effects are of a widespread nature.

The continuous tachycardia before excision of the pheochromocytoma was probably a response, in part, to sympathetic stimulation by adrenalin, and, in part, to the increased oxygen consumption. After operation the heart rate returned to normal.

The persistent elevation of blood pressure (average, 190/130) before operation was not the result of permanent changes in the vascular tree, because the pressure returned to normal after operation. Although the tumor from which this subject was suffering supplied the circulation constantly with increased amounts of adrenalin, it apparently was capable of flooding additional amounts into the circulation, because there occurred sudden rises in systolic pressure from the usual level of 190 mm. Hg to 260 mm. Hg, and in the diastolic from 130 mm. Hg to 150 mm. Hg.

The circulation time (arm-to-tongue) was shorter before operation (11.3 seconds) than after operation (13.6 seconds and 13.8 seconds). Patients with thyrotoxicosis, with preoperative basal metabolic rates comparable to this patient's (+48 per cent), had circulation times which were two to four seconds shorter.⁵ The velocity of blood flow may have been less rapid in this subject before operation because of the resistance offered to blood flow by vasoconstriction.

SUMMARY

(1) Using a method which Stewart and Jack⁴ and Stewart and Evans^{5, 6} employed previously, measurements were made of the peripheral blood flow, and certain other data were collected, on a patient with an adrenal pheochromocytoma, before operation and at intervals for one year afterward.

(2) Before operation, at a time when the basal metabolic rate was high, there was a marked relative decrease in the peripheral blood flow in c.c./M²/min. After operation the basal metabolic rate fell to normal, and an increase in peripheral blood flow occurred. The decreased peripheral blood flow before operation was attributed to hyperadrenalemia.

(3) The circulation time was shorter before operation than afterward.

(4) The low average skin temperature and the high rectal temperature before operation were interpreted as being brought about by decreased peripheral blood flow and vasoconstriction, with resulting inefficiency in heat loss and increased heat storage. As an explanation for the periods of marked sweating, these observations suggest that the organism increased heat loss by the cooling effect of evaporation. After operation the skin and rectal temperatures returned to normal.

(5) No definite relationship was observed between the temperature of the hands and feet and average skin temperature during any of the observations. On the other hand, all temperatures rose after operation.

(6) The blood pressure and pulse rate were markedly elevated at first and returned to normal after operation.

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TUBERCULOUS ENDOCARDITIS

MARGARET BEVANS, M.D., AND SAM A. WILKINS, JR., M.D.
NEW YORK, N. Y.

AT BELLEVUE HOSPITAL we have recently had occasion to observe a case of tuberculous endocarditis superimposed upon an unusual congenital defect of the aortic valve, associated with certain changes possibly rheumatic in origin.

CASE REPORT

A. R., a colored man, 17 years old, was admitted October 13, 1940, complaining of gradually increasing dyspnea over a period of one and one-half years. This had become more pronounced during the preceding three or four weeks.

The patient denied having any illness previous to two years before admission; however, examination of the outpatient records of Harlem Hospital revealed that in March, 1936, he had applied for treatment there because of a "cough and cold." At that time he admitted having frequent attacks of epistaxis and was found to have a mitral murmur. During 1937 and 1938, because of pains in the knees and in the joints of the hands, he attended the orthopedic clinic, where a diagnosis of arthritis was made in 1938. He was hospitalized and tonsillectomy was done. There was no history of headache, hemoptysis, cough, or disturbances referable to the genitourinary system.

One and one-half years before admission to Bellevue Hospital the patient noted shortness of breath on climbing two flights of stairs. The dyspnea increased slowly, and he began to notice palpitation of the heart on exertion. On one occasion, about a year prior to admission, he experienced pain in the epigastrium; this gradually subsided. Ten months before we saw him he had muscle and joint pains and was not thereafter allowed to take part in sports at school. For several weeks before admission he had been occasionally short of breath even while at rest. There was no history of edema of the ankles, hemoptysis, or precordial pain during this time, nor of chills and fever. At no time had he received digitalis. He thought he had lost some weight.

Physical examination revealed a well-developed, fairly well-nourished young Negro. He was dyspneic but not cyanotic. Apparently he was in no acute distress, sitting quietly in bed. His temperature was 102° F., the pulse rate was 129, the respiratory rate, 36, and the blood pressure, 140/80. The skin was smooth, warm, and moist, and the mucous membranes appeared to be slightly pale. The lungs were resonant throughout and no râles were heard. There was a marked precordial heave which moved from apex to base, together with a systolic thrill over the apex and in the second left intercostal space anteriorly. The point of maximum impulse was in the left fifth intercostal space in the midaxillary line, where, also, the left border of cardiac dullness was found. In the third left intercostal space the cardiac dullness extended eight centimeters from the midsternal line. At the apex, loud, low-pitched, prolonged diastolic and presystolic murmurs blended with a systolic murmur. It was difficult to distinguish the systolic murmur which was heard over the aortic area from that over the apex. The pulmonic second sound was loud and booming, and of greater intensity than the

From the Second (Cornell) Medical Division, the Laboratories of Pathology at Bellevue Hospital, and the Department of Medicine, Cornell University Medical College.

Received for publication July 22, 1941.

aortic second sound. No friction rub was heard in any part of the chest. Neither the liver nor the spleen was palpable. The extremities showed no clubbing or edema, and there was no enlargement of the lymph nodes.

Examination of the urine was negative; it was acid, and the specific gravity was 1.015. The hemoglobin was 14.5 grams, the erythrocyte count, 5.9 million, and the leucocyte count, 13,000. The blood smear appeared to be normal; there were 62 per cent polymorphonuclear leucocytes, 4 per cent transitional cells, 30 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophiles. The blood Wassermann reaction was negative, the nonprotein nitrogen was 43 mg. per cent, and the blood sugar was 83 mg. per cent. The estimated sedimentation rate was 0.1 mm. an hour.

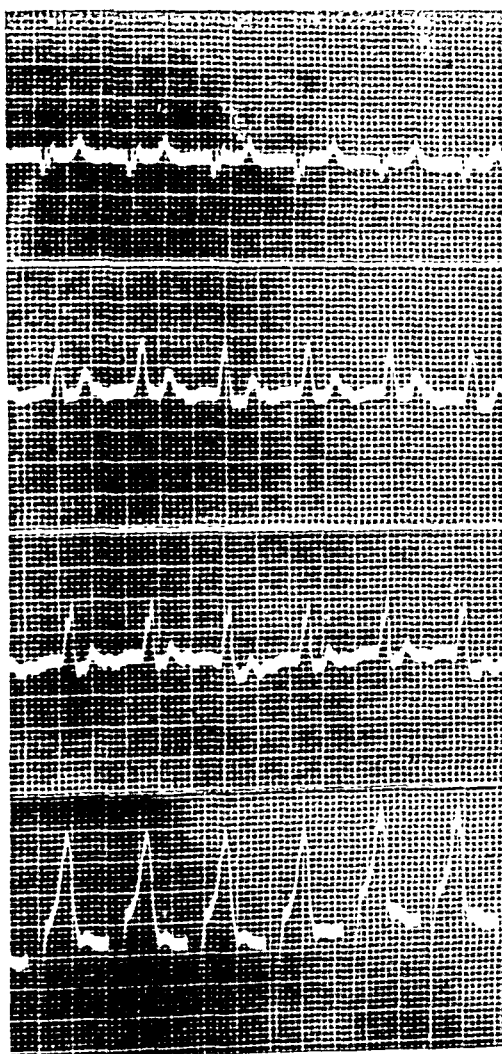


Fig. 1.

The electrocardiogram (Fig. 1) showed heart block, with a P-R interval of 0.28 sec., sinus tachycardia, and right axis deviation. In Lead I the Q wave was notched; in Lead II the R wave was slurred and the S-T segment negative; in Lead III the R wave was notched and the S-T segment negative; and in Lead IV the S-T segment was positive.

A roentgenogram of the chest (Fig. 2) showed an enlarged cardiac silhouette, centrally placed. The left cardiac border was elongated and bulging, and the right cardiac curve was accentuated. The pulmonic fields were not remarkable.

While in the hospital the patient at no time appeared to be acutely uncomfortable. On several occasions he was observed lying prone in bed, with his left side slightly elevated; when questioned about this he replied that breathing was easier when he assumed this position. His temperature ranged between 98.6° F. and 101° F., and his pulse rate, between 124 and 88. Digitalis, which was given to observe what effect it might have on the heart rate, not because of any signs of congestive failure, was of no apparent value. The patient's condition showed little change until the fifth day after admission when he had an "attack" which lasted about three minutes. Patients nearby called a nurse to see the patient, who was breathing very "heavily," with eyes rotated upward. He died a few moments thereafter.

The clinical diagnoses were active rheumatic heart disease with valvulitis, endocarditis, myocarditis, and pericarditis with effusion.

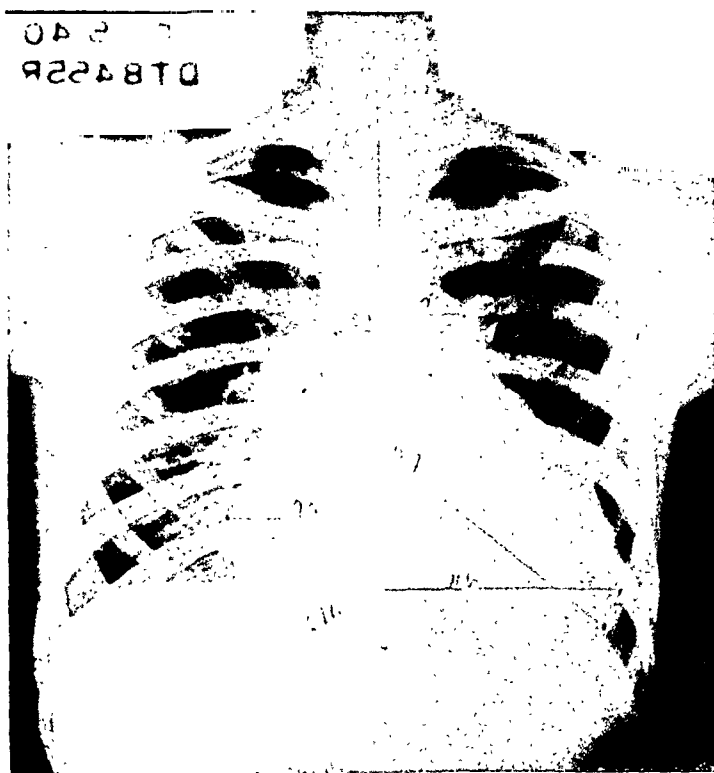


Fig. 2.

Necropsy (No. 28,473, Bellevue Hospital) was performed three hours after death. Seven hundred c.c. of serosanguinous material were found in each pleural cavity. The pleura was richly studded with gray-yellow, firm nodules about 2 mm. in diameter, some of which were surrounded by an area of hemorrhage. Similar nodules were uniformly distributed through both lungs. At the apex of the left lung there was a puckered scar. The precordial area occupied more than two-thirds of the anterior chest wall. Two hundred c.c. of exudate similar to that found in the pleural cavities were present in the pericardium. Even after its removal the heart appeared enlarged to the left, and over its anterior surface there was a granular, hemorrhagic exudate.

The heart weighed 690 grams. The left auricle was dilated. The endocardium of the left auricle was markedly thickened, and above the posterior mitral leaflet there was a conglomeration of minute gray nodules which measured about 1 cm. in diameter and 2 to 3 mm. in depth. They were firm and apparently covered by intact

endocardium. The mitral orifice was not stenotic, although both leaflets appeared fused and thickened, the posterior to a much greater extent than the anterior, so that it assumed a fusiform shape along the line of closure (Fig. 3). On section through this thickened tissue, yellowish cheesy material could be scraped from the cut surface. The chordae tendineae were slightly shortened, but not thickened or fused. The left ventricle was dilated. The aortic valve was the seat of an anomalous formation. Failure of the cusps to fuse with the ventricular endocardium for a distance of 5 cm. from their free edges produced aneurysmal dilatations which were distended with clotted blood (Fig. 4). There was no connection between these outward pouchings and the substance of the mitral valve. Immediately below their line of closure the cusps assumed a fibrous and nodular appearance. Yellowish plaques extended downward over the aortic surface of the mitral valve. The lumen of the left circumflex coronary artery, 4 cm. from its origin, was narrowed to the size of a pin point for a distance of 0.5 cm. by an endarterial process (Fig. 7). Beyond, the coronary artery showed moderate, patchy, fibrous thickening. The anterior descending ramus of the left coronary artery was involved by a similar process which, however, was less pronounced than that observed in the circumflex. The right side of the heart was apparently well preserved.



Fig. 3.

Fig. 3.—Arrows point to endocardial nodules in left auricle and swollen, deformed, posterior mitral cusp. Gloved finger near apex.



Fig. 4.

Fig. 4.—Arrows showing malformed cusp, with resulting aneurysmal dilatation. Also blood clot within sac. Note nodular, irregular surface of valve.

The aorta was smooth and elastic, and measured 7 cm. in diameter above the sinus of Valsalva, in contrast to 10 cm. at the ring.

There were 500 c.c. of clear, straw-colored fluid in the abdomen. The liver was enlarged and presented a nutmeg appearance. The spleen was about normal in size, firm, and showed numerous hyperplastic follicles, as did the mucosa of the terminal ileum and colon.

The anterior mediastinal, hilar, and paratracheal lymph nodes, as well as a few of the mesenteric nodes, were tremendously enlarged and discrete, and, on section, the cut surfaces were flecked with pin-point yellow dots which were occasionally confluent. In the confluent areas the consistency was soft and the substance was caseous. The solitary enlarged axillary node showed the same changes.

Post-mortem culture of the spleen and mitral valve yielded no growth.



Fig. 5.—Sections through posterior mitral leaflet showing (b) areas of caseation and (a) abscess composed of purulent exudate in which giant cells are seen.

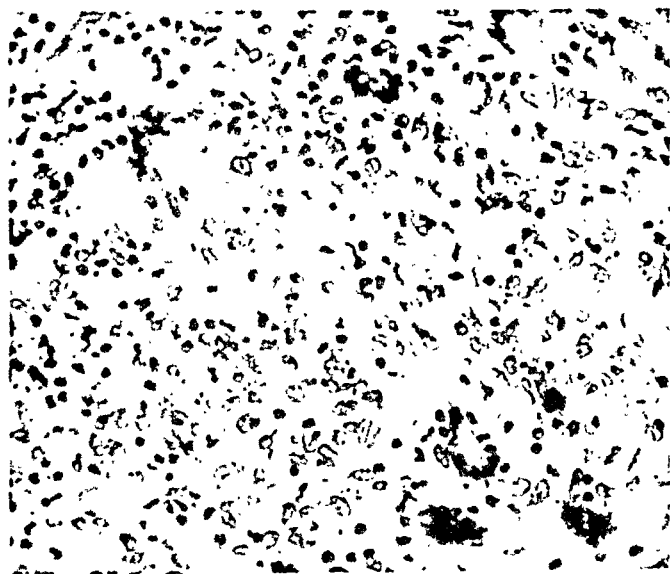


Fig. 6.—High power of area in posterior mitral leaflet showing giant cells, epithelioid cells, and a few small lymphocytes.

Microscopic examination of tissue removed from the left auricle showed that the endocardium became abruptly distended and fragmented over a mass of fibrin in which a few erythrocytes were enmeshed. This gave way to extremely vascular and edematous granulation tissue. An occasional vessel showed fibrosis of its walls, but thin-walled, apparently newly formed capillaries were predominant. Scattered diffusely through this tissue, but with a tendency toward segregation in nests, were small lymphocytes and polymorphonuclear leucocytes, together with great numbers

of eosinophiles. No Aschoff bodies or Langhans giant cells were observed. The underlying myocardium showed some congestion and a small degree of infiltration by leucocytes.

Sections through the posterior leaflet of the mitral valve showed tremendous thickening, with subendocardial hemorrhage. As in the case of the left auricle, fibrosis of vessels could be seen and was even more prominent, and the same type of granulation tissue was present. In the posterior mitral leaflet there was a widespread destructive lesion, in the center of which was a small abscess. In addition, large areas of caseation necrosis were present. In them, polymorphonuclear neutrophils were present in large numbers, together with Langhans giant cells, epithelioid cells, and lymphocytes (Figs. 3, 5, 6).



Fig. 7.—Section through the left circumflex coronary artery showing slit-like lumen due to extensive fibrosis and proliferation of intima. Note also extensive endarteritic changes in small vessels. At upper edge (a) is lowermost border of aneurysmal sac of left aortic cusp filled with caseous material.

Other sections from the posterior cusp presented a picture practically identical with the foregoing. Sections of the anterior leaflet, taken at a distance from the lesion, revealed no evidence of recent or previous damage.

Sections from the posterior cusp of the aortic valve, including part of the contents of the aneurysmal sac, revealed; perhaps, the most highly destructive lesion of all. The margin appeared to be well-preserved, but at a short distance beneath the margin the thickened fibrotic cusp was replaced by cellular and partially necrotic tissue which, in places, appeared hyalinized. An occasional giant cell of the Langhans type was found. Here, again, large numbers of eosinophiles were present. Masses of caseous material were found both replacing and attached to the cusp, as well as enmeshed in the organizing thrombus.

Sections through the left circumflex coronary artery showed, in the adjacent epicardium, dense collections of lymphocytes. Congested capillaries were numerous. The coronary artery and all of its visible branches were the seat of obliterative endarterial fibrosis which reduced their lumina to mere slits and, in some instances, to complete extinction. The muscular walls appeared hyalinized, and the intima was fibrosed. The endothelium was intact. In the same sections, which included remnants of an aortic cusp, caseation necrosis, epithelioid cells, and an occasional Langhans giant cell were evident (Fig. 7).

Sections through the interventricular septum revealed marked thickening and hyalinization, and, near the myocardium, congested capillaries and numerous small, fibrotic vessels. This scarring extended deep into the myocardium and replaced it. Diffuse myocardial fibrosis, often perivascular and accompanied by endarterial changes, was seen throughout the sections.

The microscopic changes in sections of other areas of the myocardium varied with the location. Those taken close to the base of the left ventricle showed the most marked changes, which diminished halfway through the myocardial wall. The overlying epicardium exhibited discrete collections of lymphocytes, epithelioid cells, and congested capillaries. The smaller vessels showed endarterial fibrotic changes. Similar collections of cells near a coronary vein and nerve showed, in addition, Langhans giant cells, and were obvious attempts at tubercle formation. In the myocardium, discrete collections of small round cells, resembling those in the epicardium, and perivascular fibrosis were apparent. In the wall of a myocardial vein was a raised plaque, composed of lymphocytes and epithelioid cells, that had disrupted the intima.

Sections from the apex of the left ventricle and from the right ventricle showed small areas of myocardial degeneration and fibrosis.

In numerous sections from the lungs there were small, uniformly distributed tubercles with caseous centers and a few Langhans giant cells.

The spleen showed chronic passive congestion and hyperplasia, both of the follicular cells and small lymphocytes in the Malpighian bodies. No tubercle formation was observed in the spleen.

The liver, kidneys, and adrenals were the seat of chronic passive congestion.

The intestinal sections showed lymphoid hyperplasia of the solitary follicles, but no tubercle formation.

In the lymph nodes of the anterior mediastinum and the mesentery, and in an enlarged axillary node, widespread tuberculous caseation had replaced the normal architecture. In some areas the reaction was one of proliferation, but exudation and caseation were predominant.

Sections from the lymph nodes and heart, stained by the method of Ziehl-Neelsen, revealed a few acid-fast bacilli which were morphologically indistinguishable from tubercle bacilli. In the heart valves these organisms lay in the substance of the valve. In all of the sections thus stained, even in the caseous lymph nodes, acid-fast bacilli were scarce and were found only after diligent search.

Gram-Weigert stains of the heart valves failed to show other bacteria. Sections stained by the older method of Levaditi were negative for spirochetes.

COMMENT

The history, physical examination, and laboratory data were compatible with a diagnosis of rheumatic heart disease. There was nothing to suggest an unusual clinical entity.

We feel that the case here recorded fulfills the requirements for the gross and histologic diagnosis of caseous tuberculosis of the heart valves and endocardium. In addition, it affords some support to the theory of allergic sensitization, advanced by Davie, because of the large numbers of eosinophiles in the valve lesions.

REFERENCES

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2. Mark, Jerome: Tuberculous Endocarditis of the Pulmonary Valve; Case, *Bull. Johns Hopkins Hosp.* 62-63: 415, 1938.
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Abstracts and Reviews

Selected Abstracts

Blair, H. A., Wedd, A. M., and Hardwicke, H. M.: The Normal Pneumocardiogram. *Am. J. Physiol.* 136: 523, 1942.

Pneumograms of the chest, the abdomen, the neck, and the thigh taken during suspended breathing are related to the electrocardiogram and to the venous and arterial pulses. Ejection during systole of arterial blood from the chest creates there a fall in pressure which causes collapse of the chest wall, a probable rise of the diaphragm, and aspiration of venous blood from the neck and abdomen. The effect on the abdomen is such that it also collapses. The volumes of the neck and thigh increase to compensate for the decreased volume of the trunk. During diastole, the chest and abdomen expand because venous return exceeds arterial outflow. When decrease of the volume of the chest is recorded in the same direction as increase of pressure in the artery, the pneumocardiogram of the chest is similar in form to a record of the carotid pulse. The pneumogram usually indicates the beginning of isometric contraction of the ventricles, the beginning of ejection from the chest, the beginning and end of isometric relaxation, auricular filling, and sometimes auricular contraction. It yields, in general, more information than the pulse, yet it is much easier to record. It is concluded that the low pressure of the neck veins during ventricular systole is due to the aspirating action of arterial ejection. Aspiration of venous blood is probably an important factor in promoting venous return. The rise of the venous v wave is thought to be due to ventricular relaxation. The part played by relaxation of the ventricles in producing characteristic waves in the pneumograms of the chest and abdomen and the notch in the arterial pulse is stressed. The relation of the Q wave of the electrocardiogram to the beginning of ventricular contraction and of the T wave and the second sound to ventricular relaxation is determined for a group of normal subjects. Electrical and mechanical systole are seen usually to begin very close together.

AUTHORS.

Mayerson, H. S.: The Influence of Posture on Blood Flow in the Dog. *Am. J. Physiol.* 136: 381, 1942.

Tilting of anesthetized dogs to the upright (75°) position, feet down, resulted in a consistent and marked decrease in the rate of blood flow in the femoral vein and artery and a less pronounced fall in the carotid artery and jugular vein. Changes in renal flow were less consistently observed, but in the majority of experiments were in the same direction.

L. W. ROTH.

Lebowich, R. J., Opps, F. A., and Procita, L.: Simultaneous Soap-Wax Dehydration and Infiltration of the Human Heart: A Method for Permanent Preservation. *Arch. Path.* 33: 696, 1942.

A rapid and simple technique is described for the dry preservation of the human heart without sacrifice of color through infiltration by a warm liquid soap-wax solution in a specially constructed vacuum apparatus.

It possesses the advantages of economy, through the elimination of costly museum jars and preserving fluids, and of permanence of preservation.

Tissue sections can be prepared from the finished specimen that are superior to those obtained with the paraffin infiltration techniques.

AUTHORS.

Bernstein, P., and Mann, H.: A Clinical Evaluation of Fetal Electrocardiography: A Study of 100 Cases by a New Technique and an Improved Instrument. *Am. J. Obst. & Gynec.* 43: 21, 1942.

In summarizing the results described, the following conclusions may be stated:

A fair sample, consisting of the first 100 consecutive full-term pregnancies, terminated by normal labors, was studied. In this sample, an almost equal number of parous and nulliparous, white, and Negro women of all ages, is found. Vertex presentations singularly occurred in all but four cases. The number of male and female infants was almost similar.

Constancy of method, technique, and personal error was maintained since all tests were performed by one of the authors.

A cursory outline of historical data is briefly mentioned along with the technical difficulties previously experienced.

A new technique, describing variations in position of electrodes as well as the small convenient portable electrocardiographic instrument, is described. Several complications, inherent physical disturbances, which may alter or obstruct clear recordings, are pointed out. Generally, larger, more obese women yielded inferior electrocardiograms.

Only two patients of the entire group failed to exhibit satisfactory fetal curves at some time during pregnancy.

Ninety-eight out of 100 patients showed one or more satisfactory curves. The maximum number of records of any single patient was four.

Seventy-five per cent of 153 tests performed on 100 patients showed clear-cut curves. Those which were not clear were considered negative.

No positive electrocardiograms were obtainable earlier than the fourth lunar month. In this month, 33 per cent of nine readings were positive. In the third month no records were successful.

The individual monthly percentages of positive results ranged from 53.8 to 96.5 per cent. The average of all monthly percentages, from the fourth to tenth lunar months, inclusive, was 77.86 per cent.

In the last two months combined, it is significant that a total of 48 readings yielded 96 per cent positive readings.

The fetal heart rate is no index as to the fetal sex, since both sexes averaged 148.7 beats per minute. No correlation between the rate and the color of the fetus is found.

There was a tendency for a gradual but definite decline in the fetal heart rate to the eighth lunar month; from then on to delivery, there was a slight rise. The duration of the pregnancy in any instance cannot be estimated by the rate.

Fetal and maternal rates cannot be correlated; a change in one did not necessarily accompany a corresponding alteration in the other.

The electrocardiogram furnished a reliable diagnostic test in pseudocyesis of the menopause, suspected pregnancy due to amenorrhea with a large fibroid and huge ovarian cyst, as well as a missed abortion.

Electrocardiograms successfully indicated fetal viability in four instances in which fetal movements were not felt and in which the fetal heart was inaudible.

The presence of multiple pregnancies was accurately diagnosed in one case.

A marked increase in two cardiograms taken thirty-five days apart within six weeks of labor, proved to be due to an unsuspected anomaly, gastroschisis fetalis with hydramnios.

In another teratologic birth, thoracoabdominoschisis with anencephalus, in which the apex of the fetal heart was drawn cephalad in a 180° version by congenital adhesions, the T waves were inverted. This suggests the possibility of determining a breech presentation.

Generally, fetal hearts show sinus arrhythmias and occasionally show extrasystoles and varying degrees of partial block.

Intrauterine anomalies usually produce peculiar electrocardiograms in which the rate shows a marked rapidity.

Before cesarean section is performed in instances of doubtful viability, an electrocardiogram is indicated.

Electrocardiography with the above technique and new instrument was found by us to be a practicable procedure in all pregnancies between the fourth and tenth lunar months.

AUTHORS.

Garvin, C. F.: Age, Sex and Race Relationships of Auricular Fibrillation. Am. J. M. Sc. 203: 788, 1942.

The average age of death of 207 patients with hypertensive heart disease and a normal cardiac mechanism was 52.8 years; of 57 patients with hypertensive heart disease and auricular fibrillation, 62.3 years. Patients with coronary heart disease and a normal cardiac mechanism (142) averaged 59.8 at death; 35 patients with coronary heart disease and auricular fibrillation averaged 69.1 years. Fifty-eight patients with rheumatic heart disease and a normal mechanism died at an average age of 38.4 years; 61 who had rheumatic heart disease and auricular fibrillation died at an average age of 44.2 years. All these differences seem to be statistically significant. It would appear that the average age at death of cardiac patients with auricular fibrillation is greater than the average age of cardiac patients with a normal cardiac mechanism.

No association between auricular fibrillation and sex or race was demonstrable.

AUTHORS.

Baylin, G. J.: Patent Interauricular Septum Associated With Mitral Stenosis: Lutembacher's Syndrome. Radiology 38: 1, 1942.

Two cases of patent interauricular septum with mitral stenosis are presented.

The syndrome presents a characteristic roentgenographic picture, in which enlargement of the pulmonary conus and the hilar shadows predominate, along with the right auricular hypertrophy.

AUTHOR.

Stalker, H.: Coarctation of the Aorta: A Case With Right Axis Deviation of the Electrocardiogram and Auricular Fibrillation With Some Statistics. J. Michigan M. Soc. 41: 40, 1942.

A case is presented of adult type of coarctation of the aorta, not associated with any other congenital lesion, in a male of fifty years of age who showed right axis deviation in his electrocardiogram and a markedly dilated and hypertrophied right heart. The patient had shown a left ventricular failure as evidenced by dyspnea and orthopnea since he was first seen. This would be the primary strain to be expected with coarctation of the aorta and associated arterial hypertension.

It is concluded that his right ventricular failure with right axis deviation and hypertrophied right heart must have been the natural sequence from the left ventricular failure.

AUTHOR.

Stewart, W. H., Breimer, C. W., and Maier, H. C.: **Cineroentgenographic Diagnosis of Congenital and Acquired Heart Disease.** *Am. J. Roentgenol.* 46: 636, 1941.

In addition to the elucidation of the nature of some congenital cardiac lesions, and the visualization of the cardiac chambers, various abnormalities of the great vessels have been demonstrated. Compression of the large venous trunks may be visualized. The size and course of the pulmonary arteries can be clearly shown. Mediastinal tumors and vascular structures may be differentiated. Cineroentgenography may be able to clarify our knowledge of the living anatomy and physiology of the central portion of the circulatory system. This method can be employed for educational purposes.

While up to the present it has not been possible to visualize a patent ductus arteriosus, the authors have detected certain abnormalities of the greater blood vessels as well as cardiac septal defects which would contraindicate surgical relief in a "patent ductus" detected clinically.

AUTHORS.

Rossien, A. X.: **Complete Heterotaxia Associated With Obstructive Jaundice.** *Canad. M. A. J.* 46: 572, 1942.

The clinical significance of situs transversus viscerum totalis is related chiefly to differential diagnosis, since it does not interfere with the life span or physical status of the individual.

None of the theories as to the cause of this anomaly seems to merit being accepted as conclusive. The author believes that more frequent x-ray studies will show that sex plays no part in visceral mirror transposition.

A case complicated by obstructive jaundice is presented.

AUTHOR.

Lowry, O. H., Gilligan, D. R., and Hastings, A. B.: **Histochemical Changes in the Myocardium of Dogs Following Experimental Temporary Coronary Occlusion.** *Am. J. Physiol.* 136: 474, 1942.

Dog hearts were examined chemically at various times following the termination of temporary occlusions of a major coronary artery. Characteristic increases in the water, chloride, and sodium content of the myocardium were observed. In general, there was little change in the potassium concentration.

These changes have been interpreted histochemically as denoting an increase in the proportion of extracellular fluid without demonstrable change in the muscle fibers themselves.

Occlusions lasting twenty minutes or less produced an increase in extracellular fluid which persisted four hours but not twenty-four hours. Occlusions lasting forty-five minutes produced a relative increase in the amount of extracellular tissue present both four hours and two weeks after the occlusion.

AUTHORS.

Wood, E. H., and Moe, G. K.: **Electrolyte and Water Content of the Ventricular Musculature of the Heart-lung Preparation With Special Reference to the Effects of Cardiac Glycosides.** *Am. J. Physiol.* 136: 515, 1942.

Studies of the electrolyte and water content of the heart-lung ventricle are reported.

The ventricles of the untreated (failing) heart-lung heart have: an increased water content; an increase in the wet and dry weight sodium and chloride concentrations; a decrease in the wet and dry weight potassium concentration. Cor-

rection for edema and calculation of the "extracellular water" on the basis of chloride analyses indicate that: the intracellular water and electrolyte content of the untreated heart-lung ventricles is not significantly different from normal ventricles; the average edema content is 17.5 grams per cent of the final ventricular weight and is extracellular in position; the increase of sodium and chloride content of these hearts can be accounted for on the basis of the extracellular edema formation.

The ventricles of heart-lung preparations which received therapeutic doses of a digitalis glycoside have: an increased water content which is comparable to the control heart-lung ventricles; an apparent decrease in potassium content which is larger than that found in the control heart-lung and does not appear to be accountable for on the basis of an increased edema content alone.

The ventricles of heart-lung preparations which received toxic doses of a digitalis glycoside show significant changes in their intracellular electrolyte compositions. The intracellular potassium content is decreased apparently in exchange for sodium since there is approximately a chemical equivalent increase in intracellular sodium content. The doses of cardiac glycosides used in these experiments did not significantly affect the water gain or edema formation which occurs in heart-lung ventricles.

The unphysiological factor or factors which are responsible for cardiac edema formation in the heart-lung preparation must exert their chief effect on the capillary membrane, since the electrolyte concentration gradients across the muscle cell membrane and the intracellular water content of untreated heart-lung hearts are apparently normally maintained.

AUTHORS.

Saphir, O., and Wile, S. A.: Myocarditis in Poliomyelitis. *Am. J. M. Sc.* 203: 781, 1942.

Seven patients with poliomyelitis are reported, six of whom showed evidence at autopsy of varying degrees of myocarditis. Clinically, myocarditis could have been suspected in three patients because of a sudden "turn for the worse" without apparent cause, coincident with a rise in pulse rate and cyanosis. The myocarditis was characterized histologically by foci of perivascular infiltrations of lymphocytes and neutrophils. Foci of lymphocytes were also seen just beneath the endocardium. Though the number of inflammatory cells was never very large in any one area, they were present in many blocks cut from different parts of the different parts of the myocardium. The relation of the myocarditis to the bronchopneumonia which was present in four of the seven patients is discussed. The high incidence of myocarditis in this series warrants the consideration of supportive measures. The sudden death of three of these patients may be attributed to the myocarditis.

AUTHORS.

Lisa, J. R., Solomon, C., and Eckstein, D.: Persistent Tachycardia and Pulse-Temperature Disproportion: Relation to Acute Myocardial Lesions. *Am. J. M. Sc.* 203: 801, 1942.

In cases of persistent tachycardia and disproportion between the pulse rate and temperature level the acute myocardial lesions were studied. In 100 cases presenting the phenomenon, acute lesions were present in eighty, a chronic granulomatous lesion in one. In ninety-eight cases in which the phenomenon was absent, acute lesions were present in nineteen, a chronic granulomatous lesion in one and amyloidosis in one. The relation between the pulse and the temperature appears to offer a simple and valuable index to the presence or absence of acute myocardial damage in a high per cent of cases.

AUTHORS.

Raab, W.: Abnormal Suprarenal Discharges in Angina Pectoris and Their Control by X-ray Therapy. *J. Clin. Endocrinol.* 1: 977, 1941.

Adreno-cortical (AC) compounds, which consist of adrenalin combined with cortical sterols were quantitatively determined in the blood of individuals with and without angina pectoris by chemical method.

In angina patients the blood AC level, although generally normal at rest, showed abnormally intense, sharp elevations after physical exercise. These elevations persisted for several minutes. The AC compounds which were discharged into the blood stream during physical exercise were particularly rich in adrenalin.

Therapeutic roentgen irradiation of the suprarenal glands, if successful, resulted in disappearance of the abrupt AC discharges on effort, coinciding with complete or almost complete disappearance of the subjective anginal symptoms for periods of several months.

The significance of these observations is discussed from the point of view of the theory that angina upon effort is caused by the specific anoxiating effect of sudden suprarenal discharges upon the heart muscle whose oxygen supply is inadequate due to sclerosis of the coronary arteries and their inability to dilate adequately.

AUTHOR.

Smith, C., Sauls, H. C., and Stone, C. F.: Subacute Bacterial Endocarditis Due to *Streptococcus Viridans*: A Survey of the Present Status of the Previously Reported Cures and a Clinical Study of Fifteen Treated Cases, Including Another Cure. *J. A. M. A.* 119: 478, 1942.

There has been a gradually decreasing mortality rate in subacute bacterial endocarditis since the advent of the sulfonamides.

The literature has been searched for authentic instances of cure of subacute bacterial endocarditis due to *Streptococcus viridans* and 35 reports were found. The authors of these reports were written to and follow-up notes to date have been obtained.

The clinical records of 15 patients treated by several physicians at the Piedmont Hospital and Emory University Hospital which have been tabulated show that there were 2 patients who recovered in this group.

Various therapeutic procedures have been used in combination with the sulfonamides including heparin, neoarsphenamine, hyperpyrexia by diathermy, and hyperthermia with typhoid-paratyphoid vaccine. The latter is most recent and in a small series of cases has afforded the best recovery rate. Because of increased tolerance without decreased efficiency, sulfadiazine with intravenous typhoid is probably the method of choice at the present time and should receive extensive clinical trial.

Clinical trial on larger groups of patients with the combined uses of sulfadiazine and the intravenous use of typhoid-paratyphoid vaccine should be carried out. This method has so far offered the best recovery rate, but the number of patients treated in this manner is too small to justify final conclusion at this time.

Surgical ligation must be considered for those patients having patent ductus arteriosus associated with subacute bacterial endocarditis.

AUTHORS.

Spink, W. W., Titrud, L. A., and Kabler, P.: A Case of *Brucella* Endocarditis With Clinical, Bacteriologic, and Pathologic Findings. *Am. J. M. Sc.* 203: 797, 1942.

The clinical, pathologic, and bacteriologic data are detailed for a patient with brucella endocarditis.

The patient received a total of 31 Gm. of sulfathiazole and 236 Gm. of sulfanilamide. This therapy had no effect upon the bacteremia, and only temporary clinical improvement was observed.

AUTHORS.

Yampolsky, J., and Powel, C. C.: Syphilitic Aortitis of Congenital Origin in Young Children. *Am. J. Dis. Child.* 63: 371, 1942.

The case of a colored patient 9 years of age with both a maternal and a birth history of syphilis is presented.

Pathologically the aortitis has been diagnosed as of syphilitic origin, and the case must be classified as one of syphilitic aortitis due to congenital syphilis.

AUTHORS.

Wile, U. J.: The Principles Underlying the Treatment of Cardiovascular Syphilis. *Ann. Int. Med.* 15: 817, 1941.

The fundamental principles governing the treatment of cardiovascular syphilis embrace the careful appraisal of each case with regard to the therapeutic response which might reasonably be expected from the type of lesion present.

Cases in which failure is present should receive treatment no different from that given heart failure from other causes.

Cases most favorably influenced by anti-syphilitic treatment are those in which physical signs exist without symptoms, and in which there has been little or no previous anti-syphilitic therapy.

Asymptomatic cases, in which treatment directed toward syphilis has been energetic in earlier years, may often be singled out as cases which need no treatment whatever.

The beneficial effects of anti-syphilitic treatment upon cardiovascular syphilis are in a measure the result of the treatment with the drugs of choice upon subclinical syphilitic lesions in parts of the body remote from the heart itself.

Intensive treatment, such as is given in early syphilis, is seldom indicated in the late cardiovascular sequelae. Although beneficial results may be noticed with conservative arsphenamine therapy, the heavy metals, generally speaking, are considered safer and more productive of equally satisfactory therapeutic response.

AUTHOR.

Stewart, H. J., and Evans, W. F.: Peripheral Blood Flow in Myxedema. *Arch. Int. Med.* 69: 808, 1942.

Using a method which Stewart and Jack and Stewart and Evans have employed in earlier studies, measurements were made of peripheral blood flow in 6 patients suffering from myxedema when they were first seen before treatment and again on several occasions during the course of thyroid therapy. In addition, certain other measurements of the circulation were recorded. The results are summarized as follows:

In persons in a myxedematous state when the basal metabolic rate was low, the peripheral blood flow in cubic centimeters per square meter was decreased. With an increase in basal metabolic rate toward a normal level during the administration of thyroid, a progressive increase in peripheral blood flow occurred, so that a linear relation was maintained. These changes were opposite in direction to those observed in persons with thyrotoxicosis and confirm the relation between peripheral blood flow and basal metabolic in these two diseases.

The cardiac output is decreased in patients with myxedema. How the organs share this decrease is not known, but it is now shown that the amount of blood allotted to the periphery is decreased.

The circulation time treatment was prolonged. During treatment progressive decreases took place. Shortening of circulation time roughly ran parallel to an increase in basal metabolic rate and in peripheral blood flow.

The changes in pulse rate and pulse pressure followed roughly the increases in basal metabolic rate and peripheral blood flow.

For the most part, change in the average skin temperature followed the changes in basal metabolic rate and in peripheral blood flow.

No direct relation was observed between average skin temperature and the temperature of the hands and the feet.

No constant or significant changes in rectal temperature were observed during the several periods of study of each subject.

Conservation of heat has been suggested as an explanation for the decrease in peripheral blood flow in untreated patients suffering from myxedema.

AUTHORS.

Greene, A. M., and Hurxthal, L. M.: A Postoperative Follow-Up Study of Four Hundred and Sixty-Nine Thyrocardiac Patients. *New England J. Med.* 225: 811, 1941.

Four hundred and sixty-nine thyrocardiac cases in which operation was performed from 1922 to 1937 have been followed. In the first group of 303 patients, operated on between 1922 and 1932, 164, or 54.1 per cent, are living; 122 have normal heart rhythm, and 42 continue to have auricular fibrillation. Of the second group of 166 operated cases, 128 patients are still living, 98 of whom have normal heart rhythm.

The case mortality was 4.5 per cent, and the operative mortality was slightly less than 3.0 per cent.

The incidence of recurrent hyperthyroidism in the first group followed from six to sixteen years was over 10 per cent, which shows that the incidence increases the longer the period after operation.

Although these patients are restored to normal activity for the most part, their expectancy of life based on the present follow-up falls considerably short of the predicted expectancy.

AUTHORS.

Werle, J. M., Cosby, R. S., and Wiggers, C. J.: Observations on Hemorrhagic Hypotension and Hemorrhagic Shock. *Am. J. Physiol.* 136: 401, 1942.

By the expedient of regulated hemorrhages, dogs anesthetized with sodium barbital, amytal, or chloralosane were kept in a state of severe hypotension for varying intervals, after which all the withdrawn blood (heparinized) was reinjected. Central arterial, central venous, and intrathoracic pressure changes were recorded throughout the experiments.

A continuing state of posthemorrhagic hypotension is not necessarily equivalent to shock, for in many animals (a) arterial pressures and pulses were restored to normal for many hours by reinfusion of the withdrawn blood even when such animals were on the verge of cardiac or respiratory failure, and (b) the viscera showed no pathological changes at autopsy.

If, however, both the intensity and duration of the posthemorrhagic hypotension were great enough, hemorrhagic shock developed for (a) the condition was only temporarily benefited by generous infusion of blood, and (b) the duodenal and jejunal mucosa was generally edematous, congested, and bleeding with presence of excessive fluid and blood in the lumen. Other organs showed no consistent pathological changes.

While the elusive "resistance factor" interferes with attempts to standardize the procedure for experimental purposes, our results suggest that the greatest hope

lies in creation of a preliminary period of moderate hypotension (ca. 50 mm.) followed by a shorter period of extreme hypotension (ca. 30 mm.). Using such a scheme, the minimum effective durations for these respective stages were found to be less than 90 and 45 minutes and more than 60 and 30 minutes in our trials.

We have discovered no new dynamic criteria which enables us to determine whether a period of posthemorrhagic hypotension will be followed by failure or recovery on reinfusion. Indeed, hemorrhage equal to 3 to 4 per cent body weight can produce all the changes in arterial pressure pulses seen in most severe shock due to other causes. Irreversibility after substantial infusion, admittedly unsatisfactory as a practical guide, is unfortunately the only reliable one at present.

Circulatory failure following reinfusion of all withdrawn blood developed despite an adequate blood volume and regardless of hemodilution or hemoconcentration. Augmented hemoconcentration induced by plasmapheresis had no discoverable accelerating action. The factor which precipitates the irreversible state of hemorrhagic shock resides in the cardiovascular system. Reduction of effective venous pressure did not account for the failure of arterial pressures in the majority of our animals. Since, in the majority, effective venous pressures were at or above normal levels during the postinfusion decline of arterial pressures, the deterioration of arterial pulses must be due to impairment of the heart, changes in the aorta and its elastic branches, and/or in the resistance at the periphery of the arterial tree.

The supervention of cardiac alternans during early periods of posthemorrhagic hypotension, the later tendency toward progressive slowing, the poor response to rapid infusions and the terminal rise of venous pressures suggest operation of a cardiac precipitating factor in some of our animals.

AUTHORS.

Foà, P. P., Woods, W. W., Peet, M. M., and Foà, N. L.: Effective Renal Blood Flow, Glomerular Filtration Rate, and Tubular Excretory Mass in Arterial Hypertension. Arch. Int. Med. 69: 822, 1942.

Effective renal blood flow, filtration rate, and renal tubular excretory mass have been determined for 20 patients with hypertension and for 7 nonhypertensive subjects.

The results indicate that arterial hypertension in man is accompanied by reduced renal blood flow, owing to increased resistance of the efferent glomerular vessels. However, they do not prove whether ischemia is a causal factor in hypertension or is simply one aspect of the systemic vascular disease. The relation between the function of the renal vessels and other clinical and morphologic observations is discussed. The latter include data on blood pressure, the condition of the eye-grounds, urine concentration, urea clearance, nonprotein nitrogen content of the blood and ratio of the wall to the lumen of the arterioles of intercostal tissue obtained for biopsy.

The patients are being studied approximately two weeks and six months after supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. The results of postoperative study will be reported in the future.

AUTHORS.

Kahn, J. R., and Laipply, T. C.: Frequency of Bilateral Renal Disease in Persistent Hypertension. Am. J. M. Sc. 203: 807, 1942.

From this study it is obvious that in nearly all cases of persistent hypertension with vascular disease the renal disease is bilateral. The renal involvement may be much more marked in one kidney than the other and can be so extreme as to produce a functionless or almost functionless organ. All known clinical tests of excretory function may fail to detect renal vascular disease. The weight and size of the kidney are not directly proportional to the degree or duration of the hypertension.

AUTHORS.

McLennan, C. E., McLennan, M. T., and Landis, E. M.: The Effect of External Pressure on the Vascular Volume of the Forearm and Its Relation to Capillary Blood Pressure and Venous Pressure. *J. Clin. Investigation* 21: 319, 1942.

The pressure plethysmograph was used to determine the effect of graded external pressure on the vascular volume of the forearm, for the purpose of determining the usefulness of this procedure in estimating the blood pressure in the minute vessels collectively.

With external pressure ranging from 0 to 90 mm. Hg, pressure-volume curves were determined in 20 normal subjects (a) by suddenly arresting the circulation to the forearm and measuring decrease in volume, and (b) by releasing circulation suddenly after prior arrest and measuring increase in volume during the ensuing mild hyperemia. The term "dynamic vascular volume" was used to indicate that the volume of blood in actual movement was being measured under these conditions.

In the normal forearm "dynamic vascular volumes" were greatest when external pressure was between 15 and 35 mm. Hg, becoming less at external pressures above and below this range.

To record the relation between "dynamic vascular volume" and external pressure in the form of a single numerical value, an objective method of analyzing the pressure-volume curves was adopted. The single value thus obtained was termed *Pmve* and was defined as "that external pressure at which the vis a tergo of the circulation is able to keep open the greatest collective dynamic vascular volume."

Pmve determined in the forearms of 20 normal subjects with the forearm segment at heart level and at 34° C. was 27, 21 and 21 mm. Hg by Methods I, II, and III respectively. Reasons are given for regarding Methods I and II as the most useful. In the normal subject the results by all three methods had roughly the same order of magnitude as average capillary blood pressure when determined directly.

This similarity between *Pmve* and directly determined capillary blood pressure held also when the latter was reduced by elevating the forearm or increased by known venous congestion and by depressing the forearm below heart level.

With due precaution against assuming too quickly the quantitative validity of any indirect method of measuring intravascular pressure, it is suggested that the plethysmographic method may be useful in studying the volume of blood and the pressure in the minute vessels of the forearm in clinical conditions.

L. W. ROTH.

Leary, T.: Arteriosclerosis. *Bull. New York Acad. Med.* 17: 887, 1941.

Atherosclerosis, the important form of arteriosclerosis, is distinguished from other forms of arteriosclerosis by the presence of excess cholesterol in the lesions. It is the "cholesterol disease" of man.

Excess cholesterol, i.e., visible cholesterol, is an irritant, producing lesions in the experimental rabbit (in addition to atherosclerosis) resembling those produced by intravenous silica.

Earliest lesions of atherosclerosis in the experimental rabbit and man are marked by the presence of foam cells containing cholesterol esters in the subendothelial layer of the normal arterial intima. This lesion regresses in atheroma by a mechanism of cholesterol removal. It progresses in atherosclerosis to produce the characteristic nodular lesions of the disease.

In the experimental rabbit, fed cholesterol, it has been possible to observe the esterification of cholesterol in the liver and the adrenals; deposition of these esters in liver and adrenal cells to the point of becoming a burden; engulfing of the excess esters and their removal from the liver and adrenals by Kupffer and corresponding cells; escape of these cells into the circulation; their passage of the lungs and invasion of the arterial intima. Thus are begun new atherosclerotic lesions, or accretions are made to those already started.

Excess cholesterol is the cause of atherosclerosis. Stresses determine the localization of lesions. Thyroid secretion controls cholesterol metabolism. Sex, age (time + thyroid deterioration) and heredity are modifying factors.

Diet, with limited or absent cholesterol, should prevent atherosclerosis. Vegetable oils, whose sterols are not absorbed, can be substituted for animal fats.

AUTHOR.

Sprague, H. B., and Westinghouse, W.: Arterial Occlusion in Relation to Effort With Special Reference to the Retinal Arteries. New England J. Med. 225: 1002, 1941.

Seventy-seven attacks of acute arterial occlusion in 75 ambulatory patients are described: 30 of these occurred in the retinal arteries of 29 patients, and 47 occurred in other peripheral arteries of 46 patients.

In 3 cases, the occlusion took place during rather severe effort, and in 2, a few minutes after unusual exertion; in 37, the occlusion occurred coincident with mild or very moderate effort, and in 35, when the patient was at rest either in bed or sitting in a chair.

Peripheral arterial occlusion from embolism, thrombosis, or endarteritis rarely occurs during unusual physical effort even in patients with cardiovascular disease of a degree compatible with quite strenuous exertion. In this series, such occlusion occurred approximately fourteen times as often when the patient was at complete rest as when engaged in the ordinary exertions of his usual life.

In approximately half the entire series of arterial occlusion—embolic and obliterative—the patient was physically inactive. This suggests that the conditions necessary for either embolism or thrombosis are as effective with reduced as with increased blood flow, and that the occurrence of such an accident is at least fortuitous.

AUTHOR.

Binford, C. H.: Syphilitic Aneurysm of the Superior Mesenteric Artery. Arch. Path. 33: 691, 1942.

A Negro man, aged 60, presented at autopsy a large syphilitic aneurysm of the superior mesenteric artery and hepar lobatum. The Kahn reaction of the blood was positive, and *Spirochaeta pallida* was demonstrated in sections of the aneurysmal wall.

AUTHOR.

Williams, R. R., and Zeek, P.: Periarteritis Nodosa With Peripheral Polyneuritis and Hyperglycemia: A Case Record Presenting Clinical Problems. Ohio State M. J. 38: 148, 1942.

In this case the diffuse pancreatic involvement accounted for the glycosuria, hyperglycemia, and terminal peritonitis. Either the pancreatitis or the gastric ulcers furnish ample cause for the abdominal pain and vomiting. Lesions also were found which accounted for the testicular tenderness and the polyneuritis. The partial plugging of the ampulla of Vater may have caused the jaundice. The widespread involvement of the blood vessels, both in the kidneys and elsewhere, was probably the basis for the hypertension and myocardial hypertrophy.

The correct diagnosis in this case was made clinically on the basis of a generalized systemic febrile disease with manifestation referable to multiple viscera, hypertension, and progressive peripheral polyneuritis. The muscles taken for biopsy did not contain small arteries of the type usually involved in periarteritis nodosa and was therefore of no value in diagnosis. The skin biopsy, however, contained a small artery and confirmed the clinical impression. It is of interest that this positive biopsy was obtained from the area of the papulo-vesicular dermatitis over the abdomen.

AUTHORS.

Master, A. M., Dack, S., and Jaffe, H. L.: Follow-Up Studies in Coronary Occlusion. I. Degree of Recovery, Symptoms, and Physical Signs. *New York State J. Med.* 42: 413, 1942.

A detailed follow-up study of the cardiac status, as determined by symptoms and physical examination, has been made in a group of 202 patients who had recovered from an acute coronary occlusion one to six years previously.

Clinical recovery from the attack was good in one-third, poor in two-fifths, and fair in the remainder of the series. Two-fifths showed no or only slight restriction of physical activity.

Two-thirds of the patients complained of precordial pain, dyspnea, or fatigue and one-third had no symptoms of cardiac disability.

Angina pectoris occurred in three-fifths of the patients. Coronary occlusion may initiate an anginal syndrome or aggravate one previously present. On the other hand, pre-existing angina pectoris may disappear completely following the attack. The presence or absence of anginal pectoris was not influenced by the level of the blood pressure.

Dyspnea, present in over half the patients, was occasionally the only symptoms of heart failure or cardiac disability.

Weakness was common but only rarely occurred in the absence of pain or dyspnea.

Chronic congestive heart failure was present in one-fourth the patients, a much lower incidence than during the attack and of a milder degree.

Persistent diminished amplitude of the heart sounds, particularly the first apical sound, was observed in about one-half the patients. This sign may be of diagnostic value in subjects over 40 suspected of coronary disease. Gallop rhythm, a sign of a failing heart, was not uncommon.

The heart rate and rhythm were normal in the great majority of patients. Paroxysmal or permanent auricular fibrillation occurred in only 5 patients. The rarity of arrhythmias in this series is in marked contrast to their frequency in the acute stage of coronary occlusion.

Hypertension, which had been present in two-thirds of the patients prior to the acute attack, returned or persisted in only one-third of the group following recovery. Although hypertension did not influence the frequency or severity of angina pectoris or the frequency of subsequent attacks, it was more common in those who developed heart failure and in those whose clinical recovery was poor.

One-half of the patients resumed their former occupations, either full or part time. Inability to work was nearly always attributable to an anginal syndrome or heart failure. Mild angina pectoris or dyspnea, however, did not prevent return to work. The great majority of patients who resumed work did so within six months after discharge from the hospital.

It is concluded that at least one-third of hospital ward patients who recover from acute coronary occlusion may lead a fairly active life with no, or only slight, restriction of ordinary activities.

AUTHORS.

Reitman, N., Greenwood, W. R., and Kler, J. H.: Coronary Thrombosis in a Young Diabetic. *Am. J. M. Sc.* 203: 792, 1942.

A case of coronary thrombosis in a diabetic youth of 20 years is presented.

The relationship of cholesterol metabolism to diabetes and the premature onset of coronary disease is briefly discussed.

AUTHORS.

Espersen, T.: Studies on the Cardiac Output and Related Circulatory Functions, Especially in Patients With Congestive Heart Failure. *Acta med. Scandinav.* 108: 153, 1941.

A brief review is given of the results reported by some previous investigators in determination of the cardiac output in the clinic, especially on cardiac patients. It is pointed out that in most instances the technique has been of dubious value. In particular, in determinations carried out on cardiac patients presenting phenomena of incompensation, only minor significance has been attributable to a majority of the reported results because they were obtained with anything but a reliable technique and, hence, seemed too accidental.

The writer, therefore, has given an account of the results of his own circulatory studies. To all his experimental subjects, he has applied the method given originally by Ejnar Nielsen, and later modified by the writer. In addition, Grollman's re-breathing procedure (modified) has been employed too in a good many of these cases.

It is shown that the values obtained for oxygen utilization and thus for the cardiac output and stroke volume too in determinations on heart and lung normal subjects (Group I) after the Nielsen method are of the same magnitude as those obtained by determination after Grollman.

In 16 patients with compensated cardiac disease (Group II) the values obtained for the cardiac index after the Nielsen method were of normal magnitude in 14 cases; in the remaining two cases the values were just about at the lower normal limit.

In nine of these 16 patients it proved practicable to carry through experiments with the modification of the Grollman method suggested by Grollman, Friedman, Clark and Harrison. The results agree fairly well with those obtained after the Nielsen method.

In the compensated cardiac patients, the values obtained for the oxygen utilization are about 8 per cent (Nielsen method) and 6 per cent (Grollman method) higher than the values obtained in the normal material after the same methods—in other words, they are of the same magnitude as the average values for utilization in persons with normal circulation. But the variability of the obtained values is greater in Group II than in Group I.

Among the 27 patients with incompensated cardiac disease (Group III) examined after the Nielsen method, 15 showed a cardiac index of normal magnitude (in one case, at the upper normal limit), whereas the cardiac output was found to be decreased in the remaining 12 cases.

The average utilization for the entire Group III is respectively 35 per cent and 25 per cent higher than the corresponding values for Group I and Group II. In Group III the variability of the values for oxygen utilization is considerably greater than in the first two groups.

In 16 of the 27 patients of Group III the oxygen utilization was found to be higher than normal; in the remaining 11 cases the utilization values were of normal magnitude.

Among 12 patients with more or less pronounced cyanosis 4 showed normal oxygen utilization and normal cardiac output.

Albuminuria was present in ten of the patients in Group III. In five of these cases the cardiac output was found to be decreased; in the remaining five the cardiac output was normal.

For examination of incompensated cardiac patients the Nielsen method is superior to the Grollman method and its modifications, not only theoretically but also technically. Among the 23 of the 27 patients in Group III on whom the writer tried to carry out the Grollman determination, only 13 were able to perform the breathing

technique in a fairly serviceable degree. In 9 of these cases the results obtained after the two methods agreed fairly well.

The experimental results here presented go against the forward-failure hypothesis. Theories based on "back-pressure" are compatible with the experimental results here reported.

AUTHOR.

Lilienfeld, A., and Berliner, K.: Duplicate Measurements of Circulation Time Made With the Alpha Lobeline Method. Arch. Int. Med. 69: 739, 1942.

One hundred duplicate measurements of circulation time were made, with alpha lobeline hydrochloride used as an agent. The interval between tests varied from fifteen to sixty minutes.

Considerable differences in the results of the duplicate tests were observed in many instances. In only 3 cases were identical results obtained. In 85 cases the differences varied from 3 to 199 per cent, with an average variation of 29 per cent. The result of the second test was higher than that of the first just as frequently as it was lower. In 12 cases the second injection failed altogether to produce cough.

The factors which may have been responsible for the variations in results are discussed.

Differences in the results of duplicate tests were greatest in patients suffering from congestive heart failure. Other investigators using different methods reported the same observation. Tests of circulation time in general and the alpha lobeline test in particular should not be relied upon to evaluate the progress of a patient with congestive heart failure unless the changes shown by these tests are marked.

AUTHORS.

Wiggers, C. J., and Werle, Jacob M.: Cardiac and Peripheral Resistance Factors Determinants of Circulatory Failure in Hemorrhagic Shock. Am. J. Physiol. 136: 421, 1942.

Dogs under morphine-barbital were bled until a marked state of hypotension was maintained for several hours. At the end of such a period the withdrawn blood (heparinized) was reinjected. A state of shock was considered to exist when such reinfusion failed to maintain arterial pressures for at least three hours and the upper intestines showed hemorrhagic changes at autopsy.

Cardiometer curves were recorded optically with aortic and venous pressures, and simultaneously on a kymograph as well. Changes in cardiac behavior were assessed from critically evaluated optical volume curves. Total peripheral resistance (TPR) was calculated from $\frac{\text{mean pressure} \times 1332}{\text{cardiac output/sec.}}$ by use of calibrated drum records.

Experiments on 11 dogs consistently showed decreases in stroke and minute volumes during post-hemorrhagic hypotension and postinfusion failure, but the manner in which such reduction was occasioned differed. In one group, decrease in stroke was accompanied by decreasing venous pressures, in another it developed despite an elevation. Analyses of volume curves indicate that the capacity of the ventricles to respond to a given venous pressure (stretch) is reduced and that such hypodynamic action is masked when venous pressures decline concurrently. Prolonged reduction in coronary flow during severe hypotension is suggested as the cause. Our results strongly suggest that reduced capacity of the myocardium to respond to given venous pressures is one of the factors which precipitates an irreversible circulatory state.

In the majority of animals TPR increased during the period of posthemorrhagic hypotension as well as after infusion, regardless of whether irreversible failure supervened or not. Such increase was never maximal, for stimulation of pressor nerves temporarily increased TPR tremendously. Dogs that showed little recovery of arterial pressure after initial hemorrhage, and some of those that developed rapid circulatory

failure after reinfusion showed no increase in TPR. Consequently, our conclusion that development of hemorrhagic shock is not contingent on existence of high or low TPR. Persistence of an augmented TPR seems to retard rather than facilitate the development of hemorrhagic shock. Failure of a compensatory increase in TPR may be a second precipitating factor in creation of an irreversible state.

L. W. ROTH.

Burch, G. E., Cohn, A. E., and Neumann, C.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Finger Tip, Toe Tip, and Posterosuperior Portion of the Pinna of Resting Normal White Adults. Am. J. Physiol. 136: 433, 1942.

The spontaneous variations in volume of the tip of the right index finger, the tip of the right second toe and the posterosuperior portion of the right pinna of 12 normal white adults have been studied quantitatively. All parts have undergone continuous variations in blood volume which consist of at least five separate rhythms. The effects of the heartbeat and respiration were reflected in the pulse waves and respiratory waves respectively. The three other waves were arbitrarily named alpha, beta, and gamma.

The mean frequency of the alpha waves was 7.9 per minute in the finger tip, 7.7 in the toe tip, and 8.6 in the pinna. The mean volume of the deflections was 14.5 cu. mm. per 5 c.c. of finger, 7.1 cu. mm. per 5 c.c. of toe and 6.6 cu. mm. per 5 c.c. of pinna. The frequency of the beta deflections varied from one to two per minute and the size from 5 to 60 cu. mm. per 5 c.c. of tissue. The number of gamma deflections varied from one to eight per hour and the volume from 50 to 350 cu. mm. per 5 c.c. of tissue.

The alpha waves obtained from the finger tips of the 12 subjects fell into three types. In type I (5 subjects) the deflections were relatively small and varied very little in size. Type III (6 subjects), on the other hand, showed a wide spread in the sizes of the deflections, many being large. Type II waves, found in a single subject, were intermediate between those of type I and type III. The subjects with type I were phlegmatic and stable while those with type III were excitable and exhibited wide fluctuations in mood.

L. W. ROTH.

Neumann, C., Cohn, A. E., and Burch, G. E.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Tips of the Fingers and Toes and Posterosuperior Portion of the Pinna of Hypertensive Patients and Senile Subjects. Am. J. Physiol. 136: 451, 1942.

The spontaneous variations in volume of the peripheral blood vessels of the tip of the right index finger, the tip of the right second toe, and the posterosuperior portion of the right pinna were found to be about the same in patients with diencephalic hypertension as in those with renal hypertension. The configurations and other characteristics of the 5 types of rhythm in the blood vessels of these parts were found to be essentially the same as those described as occurring in normal subjects. In no instance were the alpha waves of these patients of type I. Of the 13 patients with hypertension, 10 exhibited type II waves, and 3, type III. All were emotionally unstable and excitable.

In senile subjects the 5 types of rhythmic spontaneous variations were also about the same as in the normal subjects and in the patients with hypertension, with the exception of the volume of the pulse waves of the toes which was smaller. Such small waves are probably due in large part to arteriosclerotic changes. The alpha waves in all of the senile subjects were of the stable variety, type I. Whether this is due to a sluggish psychosomatic state so well known in senile individuals and also whether individuals who are emotionally stable and not easily excitable live longer is a problem which was not studied.

L. W. ROTH.

Neumann, C., Cohn, A. E., and Burch, G. E.: A Study of the Relationship Between the Pulse and Alpha Waves of the Tips of the Fingers and Toes of Five Adults. *Am. J. Physiol.* 136: 448, 1942.

Simultaneous alpha deflections and pulse waves in the finger tips were concordant in 34 per cent, and in the toe tips in 71 per cent. The range was 22 to 50 per cent in the finger tips and 62 to 76 per cent in the toe tips. In the finger and toe tips simultaneous alpha waves were concordant in 56 per cent, the range being 50 to 62. The pulse waves were concordant in 45 per cent. Forty-five per cent of the simultaneous variations in the size of the pulse waves in the finger and toe tips were concordant.

AUTHORS.

Wood, E. H., and Moe, G. K.: The Measurement of Edema in the Heart-Lung Preparation. *Am. J. Physiol.* 136: 506, 1942.

The average ventricular weight/body weight, and lung weight/body weight ratios from eighty-five heart-lung preparations have been compared with similar ratios from normal dogs. The differences found in the average ratios indicate that on the average 18 per cent and 60 per cent of the final heart-lung ventricular and lung weights respectively are edema fluid.

Satisfactory agreement was found between the edema calculated from cardiac chloride analyses and the edema determined by the weight increase of four blood-perfused Langendorff dog hearts.

The average ventricle weight/body weight ratios of 23 heart-lung hearts corrected for edema on the basis of chloride analyses was not significantly different from normal.

The edema content of heart-lung hearts cannot be adequately corrected for edema on the basis of tissue water content. Concentrations of tissue constituents of this or similar preparations are of little significance if expressed on a dry or a wet weight basis.

In the majority of heart-lung preparations a positive correlation exists between the relative magnitudes of cardiac and lung edema which occurs. This constitutes an indication that similar factors are responsible for the edema formation in the two organs.

The major part of the edema fluid which accumulates in heart-lung hearts appears to be extracellular in position.

AUTHORS.

Hertzman, A. B., and Roth, L. W.: The Vasomotor Components in the Vascular Reactions in the Finger to Cold. *Am. J. Physiol.* 136: 669, 1942.

The vascular reactions in the finger to chilling have been examined by means of the photoelectric plethysmograph. Analysis of these reactions was concerned with the role of the vasomotor reflexes.

The initial immediate constriction on application of cold is due to vasoconstrictor reflexes on which is superimposed somewhat later the direct constrictor action of cold. Evidence:

1. Accompanying constriction occurs also in the warm control fingers of the same and opposite hands, but the constriction is usually more intense in the chilled finger.

2. If a vasoconstrictor reflex is not elicited in the control fingers by an application of moderate cold, the constriction in the chilled finger occurs in a gradual progressive manner, as in the forehead skin, due to the direct constrictor effect of cold on the vessels.

The reactive dilatation which follows in the chilled finger within three to eight minutes after the application of cold, occurs independently of the vasomotor system.

Evidence:

1. The dilatation may be limited to the chilled finger and may occur there when the vasoconstrictor tone is high in the control fingers.

2. Vasoconstrictor reflexes were elicited in the chilled finger during the reactive dilatation in some experiments, while in other instances definite evidence of vasoconstrictor paralysis in the chilled finger was obtained.

L. W. ROTH.

Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation. *M. Clin. North America* 26: 943, 1942.

The presence of fluorescein in the tissue can be easily determined by its fluorescence under filtered ultraviolet light of a certain wavelength. This method which was first published by one of the authors in 1931 for directly and objectively determining the circulation time can also be used for establishing the presence or adequacy of local circulation. In regard to the first it is an objective method devoid of the defects of other procedures, in respect to the second it seems to possess greater delicacy and wider utility than the injection of radiopaque whose field of application is naturally rather limited.

The new objective method for determining the circulation time yields the following values: Normal adults range from 15 to 20 seconds with an average of 17.1 seconds in eighty-nine patients from arm to lips, in cardiac failure the time varies from 20 to 68 seconds (average 39) although 10 per cent of seventy-eight patients had a normal reading; hyperthyroidism was always associated with a shortened circulation time, 7 to 14 seconds (average 10.6 seconds in thirty-six cases). Neither Lugol's solution nor operation immediately induce a reversion to normal, despite a favorable influence on the basal metabolic rate by these measures. Eight of nine cases of hypothyroidism showed a prolonged circulation time of 21 to 34 seconds (average 26 seconds).

Although the dye can be used to determine the circulation time in all types of experimental animals without recourse to anesthesia and hence permits studies of the permeability of vessels under the influence of drugs, this has not been discussed at any length in this clinical paper.

The intestine of experimental animals and man shows an intense fluorescence after the intravenous injection of fluorescein and ultraviolet illumination of the intestine. Incarcerated portions of the bowel do not give this emission; the adequacy of the blood supply to the viscus, after liberation from incarceration, can be immediately ascertained. Clamping of the mesenteric arteries may cause infarction which can be demonstrated by the absence of fluorescence in the area affected. The importance of these observations hardly requires emphasis.

Finally the skin can also be made fluorescent: the portions of the extremities not supplied by blood remain dark rather than fluorescent. The application of this diagnostic aid in peripheral vascular disease has been shown by an illustrative case of diabetic gangrene; inadequate blood supply is shown by diminished fluorescence.

AUTHORS.

Hertzman, A. B., and Roth, L. W.: The Reactions of the Digital Artery and Minute Pad Arteries to Local Cold. *Am. J. Physiol.* 136: 680, 1942.

A. The selective effects of local cold on the terminal pad vessels and the digital artery of the chilled finger were demonstrated by means of photoelectric plethysmographs.

The digital artery does not participate in the vasoconstrictor reflexes elicited by the cold. Its later constriction during the continued application of cold appears to be due to the direct effects of the fall in temperature on the artery.

The reactive dilatation which appears during the application of cold is limited to the minute pad vessels and does not involve the digital artery until the resultant rise in finger temperature permits relaxation of this artery.

B. The effects of these reactions on the propagation of the pulse in the finger's arterial system were studied by recording the pad pulses with high frequency galvanometers.

In the usual experiment, the time relations and form of the pad pulses in the chilled finger were altered only moderately and in the direction which could be predicted from the relative participation of the pad and digital arteries in the reactions to cold.

In a few normal subjects, the reactive dilatation produced a pad pulse similar to that seen in chronic hypertension, thus suggesting that one of the factors responsible for the change in pad pulse form in hypertension may be the shunting of blood through direct arterio-venous communications.

L. W. ROTH.

Montgomery, H.: *The Effect of Drugs on the Circulation in Normal Hands and Feet.* Am. J. M. Sc. 203: 882, 1942.

Measurements of digital blood flow were made in normal subjects given vasodilator drugs. Consideration was given to the normal factors influencing blood flow, i.e., food, environmental temperature, and exercise. The approximate effectiveness of various normal and operative procedures and drugs intended to increase peripheral blood flow are indicated.

A study of the influence of several promising drugs and other factors upon digital blood flow in normal subjects shows that digital blood flow is augmented by these agents in the following order of intensity: (1) heat to the body sufficient to raise the body temperature slightly; (2) alcohol by mouth, such as whisky in doses of 2 to 6 ounces; (3) food; (4) papaverine intravenously; and (5) mechohyl by mouth. The approximated optimum doses and routes of the drugs are given.

Certain powerful vasodilator drugs decrease peripheral blood flow, probably because they have selective vasodilator action elsewhere or because they induce peripheral vasoconstriction by the carotid sinus reflex: amyl nitrite by inhalation, mechohyl (12 mg.), and doryl by hypodermic (0.5 mg.). In these instances the blood pressure falls.

AUTHOR.

Boyer, N. H., and White, P. D.: *Right-Upper-Quadrant Pain on Effort: An Early Symptom of Failure of the Right Ventricle.* New England J. Med. 226: 217, 1942.

We have recently encountered 4 patients in whom right-upper-quadrant pain, precipitated by exertion and relieved by rest, has been the presenting symptom of early right-sided heart failure. It is evidently due to acute congestion of the liver and is comparable to dyspnea on effort in early left-sided heart failure.

Direct questioning of a group of 40 patients who already had clinically evident right-sided failure, or were likely candidates for it, revealed that the pain had been present at some time in about 45 per cent. It is a symptom to which the patient rarely attaches much significance, since it is usually of little severity and is overshadowed by more uncomfortable symptoms.

If the symptom is sought as diligently as the history of dyspnea on exercise, it may be found to be a fairly common and reliable warning of weakness of the right ventricle.

AUTHORS

Book Review

DER MYOKARD INFARKT, ERKENNUNG, BEHANDLUNG UND VERHÜTUNG, BDI OF KREISLAUFBUCHERER (DEUTSCHE GESELLSCHAFT FÜR KREISLAUFFORSCHUNG): By Max Hochrein. Theo. Steinkopff, Dresden u. Leipzig, 1941, second edition, 278 pages, 58 illustrations.

This book brings before the American cardiologist the views of one of his best informed German colleagues. It cannot be recommended for the graduate student, for it fails to include many important recent contributions, and it accepts many points which are not generally accepted in this country. It clearly shows how quickly the chasm produced by the war has made itself felt, and also how rapidly our knowledge in this field is growing. In some respects the book is already obsolete.

A brief but comprehensive historical review is followed by a discussion of the incidence of myocardial infarction and a good description of the anatomy and innervation of the coronary arteries and their normal physiology. In this field, the author has made notable contributions. He takes issue with Anrep, who states that systole acts as an impediment to the coronary circulation. He also discusses the lung as a physiological blood depot and reviews experimental coronary occlusion.

The description of the pathological anatomy does not include the recently discovered prodromal changes which occur in the wall of the artery and which are of fundamental importance for our understanding of the whole problem.

The remaining three-quarters of the book contain the clinical aspects of the subject. The author places great emphasis on spasm as an immediate cause of coronary occlusion. He attributes this to a constitutional disturbance of the vegetative balance. As secondary causes he accepts focal infection (though without conclusive evidence), nicotine, coffee, and excitement. The part played by effort is uncertain. Although he quotes Master, Dack, and Jeffe's analysis of activities associated with the onset of acute coronary occlusion he ignores their conclusions in his discussion. Among his patients, the coincidence of diabetes and coronary occlusion is not increased.

Hochrein concludes that myocardial infarction does not always result from coronary sclerosis and thrombosis, but often from a functional disturbance of the coronary circulation.

There follows a discourse on the medicolegal aspects of myocardial infarction. Extraneous factors, e.g., excitement and sudden effort, are accepted as causing myocardial infarction. While the author duly distinguishes between predisposing and precipitating factors, he further distinguishes between such precipitating factors as are peculiar to the patient's occupation, and such as accidentally happen while the patient is at work, e.g., climbing stairs or running to catch a streetcar. Compensation is not awarded in these cases. This section should be read by all interested in forensic cardiology.

In the symptomatology the classical picture is sharply drawn and so are many atypical ones. The author states (p. 202) that at the time the book was written no studies had been published throwing light on the prodromal symptoms which are so important in studying the pathogenesis of myocardial infarction. The chest leads have not been given the attention which we believe they deserve, nor is the time relationship between the symptoms and the electrocardiographic changes fully discussed.

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